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VENOGRAPHY OF THE INFERIOR VENA CAVA

by

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We reported in 1956 our experiences in the roentgen examination of the inferior vena cava (cavography) in expansive retroperitoneal processes. Following some minor modifications the method described at that time was found to be extremely satisfactory and since then we have examined the inferior vena cava in a large number of cases both with and without various types of pathologic changes. In view of our further observations we now consider it worth while to present our findings in the total series.

Technique

We continued to use bilateral percutaneous catheterization of the common iliac vein by SELDINGER's method. Simultaneous bilateral injection of contrast medium was considered desirable to ensure complete contrast filling of the vena cava and for this purpose we employed a GIDLUND syringe fitted with a branched tube. Simultaneous bilateral manual injection with two syringes yielded virtually identical results, but required two operators. The contrast medium consisted of Urografin 30 %. This low concentration was found to be suitable since admixture of the blood and contrast medium then readily occurs; only occasionally was it necessary, and then in obese patients, to use higher concentrations.

In the early cases we directed the patients to strain during the injection of the contrast medium (Valsalva's manoeuvre), but we found that during this procedure the cranial part of the inferior vena cava frequently showed incomplete contrast filling, thus precluding evaluation of any deformities in that region. When injections were given during Valsalva's

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manoeuvre, the sacral and lumbar veins were often contrast-filled although there was no organic obstruction of the vena cava. In injections without Valsalva's manoeuvre such filling usually pointed to an obstruction of the vena cava or of the common iliac vein on one side or the other. Valsalva's manoeuvre was generally associated with slight or moderate dilatation of the caudal part of the vena cava, and this probably enhanced the possibilities of demonstrating expansive processes in that region. Since, however, we found that it was more important to examine the cranial part of the vein we ignored this comparatively slight asset. At the present time we instruct the patient to hold his breath without straining — which is done by applying a clamp to the nose — and then to close the mouth midway between expiration and inspiration; in this way straining is usually avoided.

In order to study the flow in the vena cava during the injection of contrast medium we examined a few cases with the use of a film changer, taking anteroposterior and lateral projections at the rate of two frames per second in each direction. To lessen the danger of thrombosis, all patients were ambulatory after the examination; no bedridden patients were examined.

Material

We performed venography of the inferior vena cava in 315 cases, 19 of which were examined twice or more. Of the 226 cases that were evaluated as 'normal', 57 were examined in two projections, 124 with oblique views alone, and 45 with anteroposterior views alone. In 40 of the 'normal' cases it was possible to verify by various means that no pathologic changes existed in the vena cava region. Of the 89 cases that were considered pathologic, 69 had been examined in two projections and 20 in one projection; in 42 of the 89 cases the diagnosis was malignant lymphoma, in 7 seminoma, in 6 testicular carcinoma, and in 14 uterine carcinoma. There were in addition minor groups of diverse tumours with a retroperitoneal localization. In 3 of the pathologic cases the venographic findings were confirmed at operation, and in 10 at autopsy. In a further 10 cases which had been examined repeatedly there was either regression or progression of an expansive process, which was considered to have confirmed the venographic findings.

No complications were observed.

Roentgenanatomical and physiologic considerations

KJELLBERG has pointed out that blood and contrast medium may flow together without mixing, and that in this way the blood stream may simulate filling defects and wall contours. With the present technique, in which a contrast medium was injected rapidly into both common iliac veins, the blood flow in these was temporarily stopped and, for a few seconds, the vena cava was virtually filled with undiluted contrast medium. We accordingly felt that we could evaluate the vena cava accurately from the films.

Fig. 1 a

Fig. 1 b

Fig. 2

Fig. 1. Normal inferior vena cava. a) A.p. Lateral contours sharp except at level of renal veins where blurring is caused by influx from kidneys. Vena cava mainly parallel with spine. b) Oblique. Square-cut indentation in posterior wall at level of L2 caused by right renal artery. Sagittal diameter of vena cava greater above than below.

Fig. 2. The vena cava sometimes has a gentle S-shape in elderly patients.

A comparison of the anteroposterior and oblique views and, in some cases, lateral views showed that the caudal part of the inferior vena cava between the junction of the common iliac and the origin of the renal veins had a greater frontal than sagittal diameter, and thus appeared to be flattened against the spinal column (Fig. 1). We several times observed in serial roentgenograms, during the injection of contrast medium into the iliac veins, an anterior displacement of the anterior wall of the vena cava in the region caudal to the renal veins, whereas the sagittal diameter was not changed in the cranial part of the vein protected by the liver. This

Fig. 3. The valvula venae cavae in the right auricle is occasionally demonstrated.

Fig. 4. The caudate lobe of the liver usually makes a smooth rounded impression cranially to the left.

Fig. 5. The right renal artery in some cases causes a groove in the posterior wall of the vena cava.

suggests that with an increased flow from the lower part of the body the caudal portion of the vein may serve as an equalizing reservoir, while the upper rigid portion in the liver prevents unduly great variations in the blood flow to the right atrium.

When our patients strained, contrast medium injected into the iliac veins frequently passed through the lumbar network up to the azygos system. With total compression of the vena cava a substantial part of the blood flow passes by this route through the lumbar and azygos veins (HELANDER & LINDBOM 1955). On injecting contrast medium directly into the left renal vein while the patient strained, we observed that it passed through the wide venous communication, present in most cases, between that vein and the lumbar veins into the lumbar network and up towards the azygos system. It seems probable that this may even occur under physiologic conditions. While taking no stand on those

the ories of tumor spread via the lumbar veins which have been pro-pou nded in recent years (BATSON and others), we would nevertheless poi t out that according to venographic observations there may be, unc r physiologic conditions, some blood flow from the iliac veins towards the azygos system via the lumbar network.

The cranial portion of the vena cava between the origin of the renal vei s and the heart usually in our series had an oval lumen in a plane opp site to that below the renal veins, i. e. it was flattened from the sides in p assing through the liver. It follows that in anteroposterior views the cra ial part of the vena cava was narrower than the portion caudal to the enal veins; only in exceptional cases did it have a frontal diameter whi h was greater above than below.

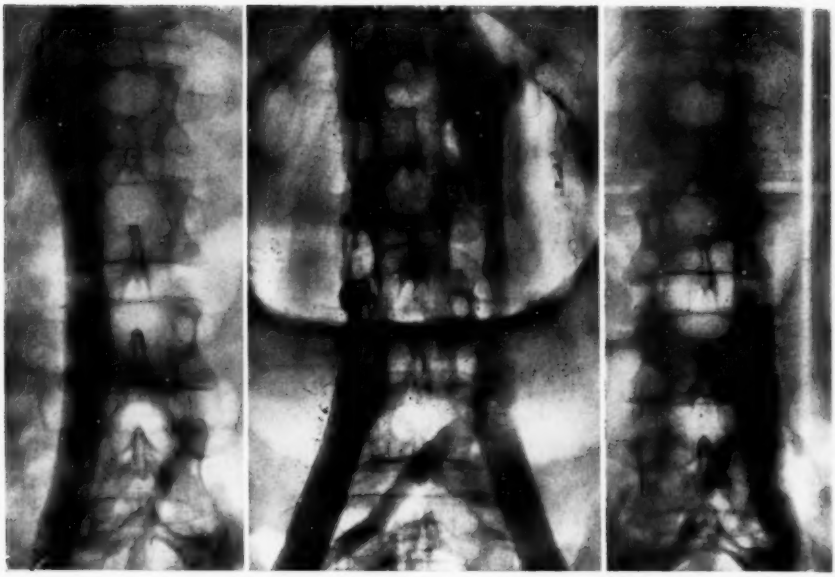
As pointed out earlier, the vena cava generally lay parallel with the lumbar spine. A gentle dextro-convex curve nevertheless occurred at the level of the third and fourth lumbar vertebrae, though in normal cases the vena cava presented a uniform diameter in the anteroposterior views. Slight tortuosity was occasionally found in the frontal plane, even in the uppermost part of the vein (Fig. 2). In isolated cases we observed the valve of the vena cava in the right auricle (Fig. 3).

The aorta and the vena cava run together in their lower parts and hence it is plausible to assume that dilatation of the aorta, which is common in the elderly, may produce an impression in the vena cava. We have inspected aortograms from 15 subjects between the ages of 60 and 70 and over, and in all the abdominal aorta was somewhat tortuous; in 10, the aorta curved convexly to the left, the curve usually being at its maximum at the level of the caudal margin of the third lumbar vertebra. The aorta therefore apparently tends to curve to the left, and thus, when elongated in old patients, will generally not produce an impression in the vena cava. In two of our cases of aneurysmal dilatation of the abdominal aorta, we nevertheless observed that the right border of the aorta reached so far to the right of the midline that it might well have caused an impression in the vena cava. Since the senile aorta usually curves to the left, this should not be regarded as a sign of an expansive retroperitoneal process; in such cases this diagnosis should be made only when the vena cava is at the same time obviously deformed. If the medial border of the inferior vena cava shows an impression, the possibility of an aortic aneurysm should be considered.

In one case of retrocaval right ureter associated with severe hydronephrosis, there was no detectable deformation of the inferior vena cava.

The caudate lobe of the liver was often discernible in anteroposterior views as a regular arciform impression in the left wall of the inferior vena cava (Fig. 4).

The defect produced by the right renal artery in the posterior wall of



a b c

Fig. 6. Double inferior vena cava. a) Injection into the right iliac vein shows right vena cava. b) Injection into both iliac veins during compression of right vena cava. The left vena cava runs to the left of the spine and crosses the midline after receiving the left renal vein. c) Injection into left iliac veins shows left vena cava.

the inferior vena cava at the level of the second lumbar vertebra was more or less marked in most cases. In oblique projections it usually produced a square-cut indentation but sometimes formed a groove (Figs. 1, 3, and 5).

In several cases scoliosis rendered difficult or impossible the evaluation of a vena cava deformity. We would point out in this connection that the pancreas lies in direct relation to the anterior wall of the vena cava, and that expansive processes in the corresponding portion of this gland could conceivably produce impressions in the wall. The root of the mesentery is also close to the anterior wall of the inferior vena cava.

The commonest anatomic anomaly is persistence of the left vena cava, so that a large vein exists on either side of the aorta up to the level of the renal veins. More rarely the vena cava lies entirely on the left side. We have observed two cases of the first-named anomaly, in which the right common iliac vein continued on the right side at the normal site of the vena cava, and the left common iliac vein passed on the left side up to the left renal vein, which joined it, and then crossed the mid-line (Fig. 6). In one case the vena cava was located to the left of the midline but

Fig. 7 a

Fig. 7 b

Fig. 8

Fig. 7. Left-sided inferior vena cava. The right ascending lumbar vein is wider than normal a) A.p. b) Oblique.

Fig. 8. Widespread retroperitoneal metastases from carcinoma of ovarian tube. Tumor at promontory compresses left common iliac vein and causes indentation in medial wall of caudal part of vena cava. Vessel encircled by tumor at L2 and L3. Lumbar veins filled because of obstruction of left common iliac vein.

passed, at the level of the renal veins, to its normal site on the right side (Fig. 7). In the presence of such anomalies it is difficult or impossible to evaluate expansive retroperitoneal processes.

Pathologic findings

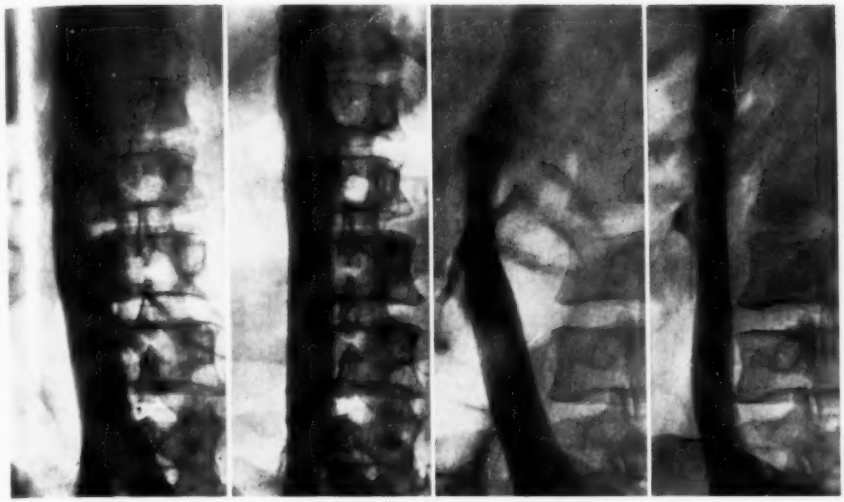
Contrast filling of the sacral and lumbar veins in cavography by the technique described, i. e. without Valsalva's manoeuvre, was found to be due to stenosis either of the vena cava or of the common iliac vein, uni- or bilaterally (Fig. 8). In some cases in which the catheter tip was accidentally advanced too far and entered the ascending lumbar vein, the contrast medium passed directly into the lumbar veins. This possibility

a b

Fig. 9. Hodgkin's disease with retroperitoneal localization. a) A.p. Vena cava pushed to the right; angulation of right and blurring of left contour. b) Oblique. Increased distance between posterior wall and vertebrae. Vena cava narrowed; filling of lumbar veins indicate obstruction of the vessel.

should therefore be ruled out first when evaluating cases with contrast filling of lumbar veins.

The great majority of our cases with expansive retroperitoneal processes had a malignant lymphoma, seminoma or carcinoma, i. e. tumors that spread in lymph nodes. We found no obvious roentgenologic difference between the retroperitoneal infiltrations associated with these forms of growths. The tumors were usually situated at the levels of the first to third lumbar vertebrae, generally at the upper border of the second lumbar vertebra (Fig. 9). This situation corresponds to the position of the aortic lymph nodes (lymphoglandulae lumbales). Cavography may reveal an enlargement chiefly of those groups of nodes which are situated between the aorta and vena cava and behind the latter. Many of the tumors in our material extended somewhat downwards, even as far as



a b c d

Fig. 10. Regression of retroperitoneal tumor (Hodgkin) after irradiation. a) and b) A.p. Before and after treatment. Slight displacement to the right and blurring of left contour has disappeared after treatment. c) and d) Oblique, before and after treatment. Tumor behind the vein has disappeared.

the inferior border of the third lumbar vertebral body; the infiltrations frequently had a distinct lower border at the inferior margin of that vertebra. They seldom extended so far caudally as to reach the level of the fourth lumbar vertebra. When, however, a tumor was found at the latter level, it was usually the lower offshoot of a major infiltration situated mainly at the second lumbar vertebra. Unusually low tumor infiltrations were observed in two cases of advanced metastases from colonic and tubal carcinomata respectively (Fig. 8). Cranially the infiltrations seldom reached the level of the twelfth thoracic vertebra. Only in a few of these retroperitoneal tumors did we find deformity of the kidneys or ureters, and hence a urographic diagnosis was impracticable.

The vena cava was usually displaced forwards and to the right in cases of retroperitoneal tumors at the level of the second lumbar vertebra. In this way it was compressed against the liver but at the same time was kept down caudally by its anchorage to the right renal vein. We often found characteristic angulation of the right vena cava contour in this region in anteroposterior views (Fig. 9). Such angulation was not observed in anyone of the normal cases.

Both the right and the left vena cava contours in normal cases in a.p. projections were quite distinct between the confluence of the iliac

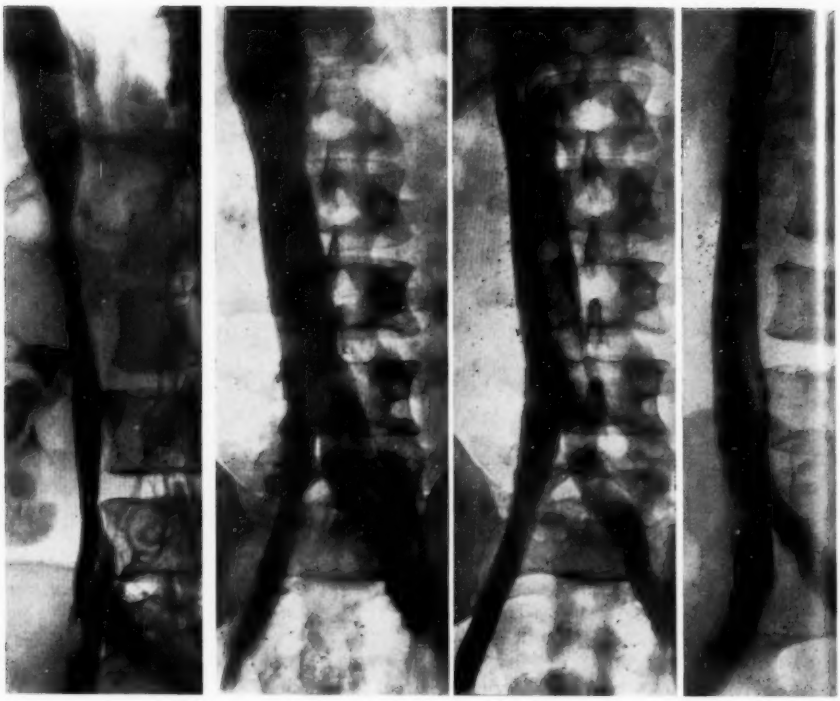


Fig. 11 Fig. 12 a Fig. 12 b Fig. 12 c

Fig. 11. Large intraperitoneal haemorrhage with compression of caudal part of inferior vena cava from in front. The intrahepatic part of the vein is of ordinary width. Filling of lumbar veins indicate obstruction of vena cava (some contrast medium in colon).

Fig. 12. Recent thrombus in the vena cava. Widespread metastases from carcinoma with psammoma body formation. a) A. p. before thrombus. b) Ten weeks later. Filling defect in vein present. c) Oblique view showing filling defect.

veins and the level of the renal veins, where the outlines were usually blurred by the blood flow from the kidneys. In most expansive processes situated between the aorta and vena cava, the left contour was indistinct in that area (Fig. 9); in addition, the majority of these cases in the oblique views showed forward displacement of the posterior wall of the vein. In some cases, however, with very slight forward displacement, the blurring of the contour was the principal sign of a tumor in the region.

Both malignant lymphomas and seminomas are often highly radiosensitive. A number of such cases were examined both before and after roentgen therapy, and in many of them considerable regression of the tumor was found (Fig. 10). In these cases cavography was usually the

only means of demonstrating the retroperitoneal metastases, and thus made adequate radiotherapy possible.

The stomach and duodenum were examined roentgenologically in connection with cavography in about twenty patients with retroperitoneal tumors. In most of them there was no detectable deformation of the duodenum. The third, or horizontal inferior, part of the duodenum passes anterior to the spinal column at the level of the third, or sometimes the fourth, lumbar vertebra, i. e. caudal to the usual situation of retroperitoneal tumor infiltrations. One case, however, in which the retroperitoneal tumor was unusually low, showed stenosis of the duodenum in association with the cavographically demonstrated neoplasm (Fig. 8). The proximal parts of the duodenum are situated too far anteriorly and cranially to be affected directly by an expansive process behind the vena cava.

Deformation of the vena cava in its passage through the liver was observed in a few cases. In one of them, in which the lumen was strikingly irregular and somewhat narrowed, liver metastases were detected by hepatic venography (HELANDER et coll.). In another case in which the liver at subsequent autopsy was found to be diffusely enlarged, there was stenosis but the contours of the cranial part of the vena cava were regular.

One patient, operated on for a retroperitoneal sarcoma, developed postoperatively a large hematoma in the peritoneal cavity which compressed the vena cava from the front so that, in oblique views, it was abnormally narrow in its caudal portion (Fig. 11). This finding was verified at autopsy a few days after cavography.

In two cases, both with carcinoma, recent thrombi were detected as filling defects in the middle part of the vena cava (Fig. 12).

In some cases the vena cava at venography was totally obstructed and a collateral circulation through the lumbar veins was observed. Autopsy in several of these revealed that a large tumor had compressed although not totally obliterated the lumen. No thrombosis was found.

Conclusions

Cavography should be performed with simultaneous injection of contrast medium into both iliac veins without Valsalva's manoeuvre. In the presence of retroperitoneal tumors the vena cava is frequently deformed. Contrast filling of the lumbar veins by the technique described points to an obstruction of the common iliac vein or the vena cava.

Retroperitoneal lymph-node metastases are usually demonstrated at the level of the second lumbar vertebra. The effect of radiotherapy in such tumor infiltrations may be discernible with repeated examinations. With the persistence of a left vena cava there is little possibility of diagnosing expansive retroperitoneal processes.

Cavography is a relatively simple and harmless method rendering possible the examination of the retroperitoneal tissues to which access is difficult.

SUMMARY

Angiography of the inferior vena cava was performed in 315 cases, pathologic changes being demonstrated in 89. The venographic appearances of the vena cava were studied in normal and pathologic cases, with special reference to retroperitoneal tumors. These are reported in detail and discussed.

ZUSAMMENFASSUNG

Eine Angiographie der V. cava inferior ist in 315 Fällen ausgeführt worden; in 89 Fällen wurden pathologische Veränderungen demonstriert. Das venographische Aussehen der V. cava wurde in normalen und pathologischen Fällen studiert; hierbei wurden die retroperitonealen Tumoren besonders berücksichtigt. Letztere werden eingehend berichtet und diskutiert.

RÉSUMÉ

Sur 315 cas d'angiographie de la veine cave inférieure, les auteurs ont trouvé des modifications pathologiques dans 89 cas. Ils ont étudié les aspects phlébographiques de la veine cave dans les cas normaux et pathologiques, et en particulier dans les tumeurs rétropéritonéales qui sont décrites et discutées en détail.

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THE DYNAMIC VARIABILITY OF THE CHOLEDOCHO-PANCREATICO-DUODENAL JUNCTION

A roentgen cinematographic investigation

by

B. Jacobsson, L. O. Lanner and *C. Rådberg*

The increasing number of biliary tract operations (4) and the high frequency of late distress following cholecystectomy (6, and others) have emphasized the importance of accurate pre- and postoperative investigations of the anatomical and functional conditions of the biliary tract. Cholangiography has for a long time been the most important method of examination and improved the possibilities of demonstrating changes such as calculi, tumours, strictures and congenital anomalies.

The terminal portion of the choledochus or the choledocho-pancreatico-duodenal junction is, from the diagnostic point of view, one of the parts the most difficult of access and at the same time from the pathophysiologic and surgical points of view one of the most important regions of the extra-hepatic biliary tract. An indispensable condition for normal drainage of the biliary and pancreatic ducts is a normal passage and capacity for functional adaptation to variations in the flow of bile and pan-

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creatic juices. Pathologic changes in the junction disturb the hepatic and pancreatic functions and thus the digestion. However, our knowledge of the normal function of the choledocho-pancreatico-duodenal junction and its sphincter mechanism is incomplete. A radiomanometric examination of the biliary tract particularly for diagnosing functional changes at the choledocho-duodenal junction was introduced by BERGERET in 1941. This region has been the subject of much attention in the French, Spanish and German literature at the end of the 1940's (1, 3, 7, 10, and others).

As pointed out by us in a previous paper (9), the terminal portion of the choledochus, especially its intramural portion, varies in appearance. Single cholangiograms therefore do not permit any definite conclusions as to the anatomical and functional conditions of the junction and its sphincter mechanism. The purpose of the present work was to elucidate the dynamic variability of the terminal portion of the choledochus and its variation both under constant and varying pressure conditions as well as under the influence of drugs.

Method

The investigation was based on postoperative roentgencinematographic studies of the bile ducts, a rubber tube or a plastic catheter being inserted into the common duct at operation and the contrast medium injected 2 to 3 weeks later. The contrast medium was infused through the choledochal drain under varying hydrostatic pressure. The flow pressure was measured by means of an electromanometer, based on the strain gauge principle (AB Elema, Stockholm), and recorded continuously in a kymograph (Mingograph, Elema). The respiration and the exposure of each frame were recorded in the kymograph simultaneously with the pressure.

The pressure values here given constitute as a rule the flow pressures and are not equal to the pressures in the choledochus, which are usually lower. (For pressure measuring, see JACOBSSON 1957.) A 35 mm film camera mounted on a Philips' image intensifier was used for the roentgencinematography; the speed was 20 to 25 frames per second. Film series lasting longer than 10 sec (= 200 frames) could not be taken as the roentgen tube employed would have been overloaded; for the same reason a break of 4 to 5 min between each series was necessary. Five to eight series of exposures were performed in each case.

The roentgen doses varied slightly, depending on the exposure data used (65 to 90 kV and 40 mA) but in no case did they exceed 50 r per patient. Sodium acetrizoate (Urokon) in a 20 to 30 % solution was used as contrast medium. The exposures were made during the infusion of the contrast medium, and, under more physiologic pressure conditions,

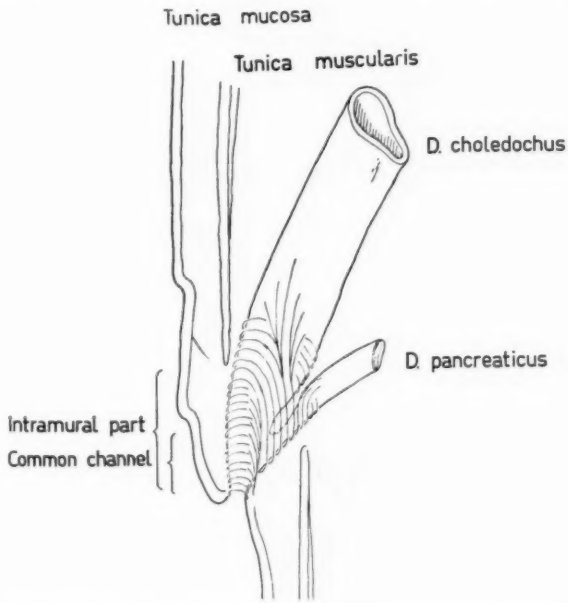


Fig. 1. Sketch illustrating the anatomy of the choledocho-pancreatico-duodenal junction.

with the contrast medium supplied to the choledochus before the exposure. The examinations were performed both before any drug was administered, after the injection of 1 cg of morphia subcutaneously, and after the tone increasing effect of morphia had been eliminated by means of 4 mg nitroglycerine perlingually (8).

Case material

Thirty-four patients in all were examined in this way. Half of these belonged to the age group of 21 to 50 years and the others to the age group of 51 to 70 years. In 30 cases the diagnosis was primary chronic cholecystitis (for definition see ref. 5), in 7 cases combined with calculi in the common duct. Two patients were operated upon for acute cholecystitis and two cases were reoperated upon because of residual calculi in the common duct. In all cases cholangiography was performed both in connection with the operation and post-operatively.

In 7 cases the urine diastasis was increased immediately following the operation, without, however, affecting the clinical course. In 3 out

of these 7 cases, reflux to the pancreatic duct was seen; in the other 26 cases reflux could be observed in 5 cases. In 9 of the cases the bilirubin index had been increased pre-operatively and in 8 of these calculi were found in the choledochus at the operation.

The films were studied first of all by projecting them at various speeds. Later on those parts which were considered to be of special interest were printed frame by frame on paper.

In all the cases examined, rapidly changing variations in the configuration of the choledocho-pancreatico-duodenal junction were demonstrated. The anatomy of the choledocho-pancreatico-duodenal junction is given as a rough sketch in Fig. 1. The choledochus penetrates the wall of the intestine obliquely and in 85 % to 90 % of the cases joins the pancreatic duct intramurally, thus creating a common channel of varying length. The sphincter muscles in the walls of the common channel, the distal parts of the choledochus, and the pancreatic duct (sphincter of Oddi) as a rule lie between the papillary opening and a point approximately 5 mm outside the intestinal wall.

In the following, five of our cases are illustrated and commented upon.

Case 1 (Fig. 2). Female, aged 40, operated upon for primary chronic cholecystitis.

The variability at a constant infusion pressure of 25 cm H_2O is evident from the views (a) to (c): a) Narrow terminal portion of the choledochus. Reflux to the pancreatic duct. b) 2.5 sec later. Contraction of the most distal portion of the sphincter with an increased reflux to the pancreatic duct. c) After another 2.5 sec. Slight constriction of the choledochus just above the common channel. Separate evacuation of the pancreatic duct to the intestine.

d) to f) After injection of morphia; infusion pressure unchanged: d) Common channel closed by contraction of the sphincter. e) 1.5 sec later. The contraction of the sphincter is less marked; narrow passage to the intestine. f) 4 sec later. Separate evacuation of the choledochus through a filiform common channel. The pancreatic duct is again partly filled and the distal part is constricted.

g) 3 sec after administration of nitroglycerine; infusion pressure still 25 cm H_2O. Common channel is wide and the distal part is open. Contrast medium flowing freely to the relaxed, paralytic intestine. The pancreatic duct is almost empty.

Comments. The infusion pressure in this series lay constantly at a comparatively low level. The configuration and the filling of the choledocho-duodenal junction varied, a variation which would seem to depend on changes in the state of contraction of the sphincter muscles surrounding the termination of the choledochus and the pancreatic duct. Contractions of the sphincter around the choledochus or the pancreatic duct just above the common channel permits separate evacuation of the ducts. After injection of morphia the tone of the sphincter muscles is increased although variations may be seen resulting in a sparse flow of contrast medium through the contracted intramural part of the channel and temporary reflux to the pancreatic duct.

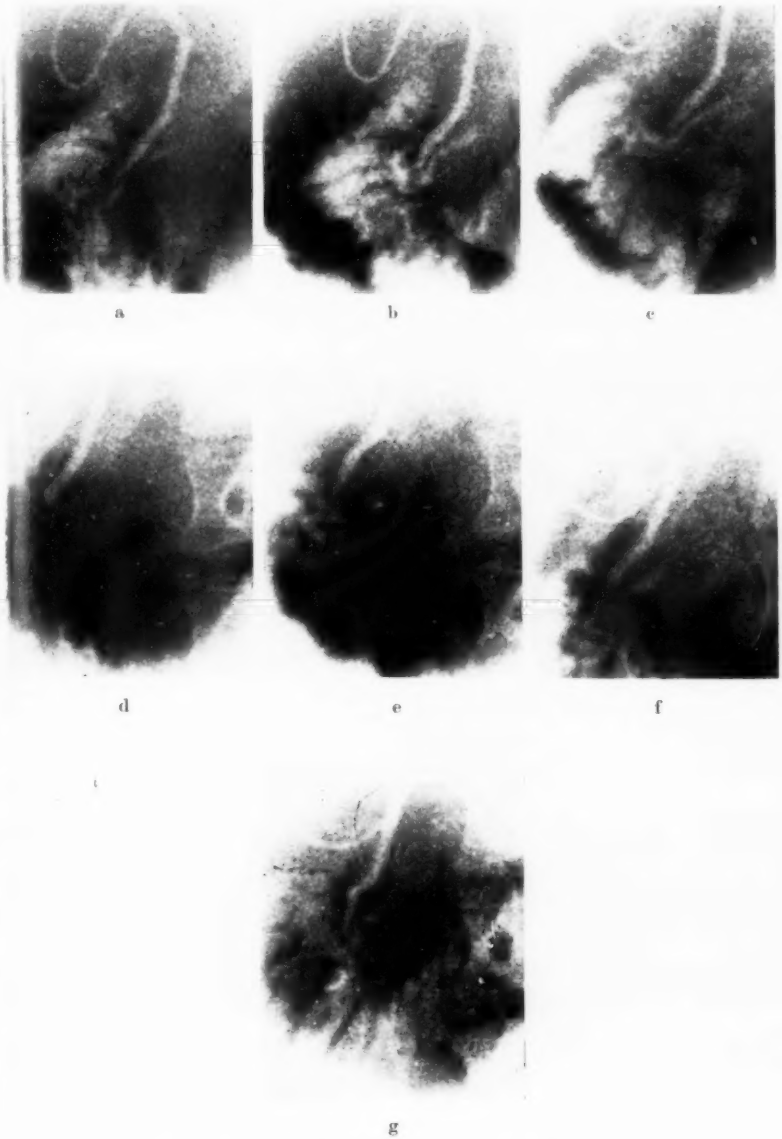


Fig. 2. Case 1. For legend and comments, see opposite page.

Case 2 (Fig. 3). Female, aged 29, operated upon for primary chronic cholecystiti.

a) to d) Choledochus pressure 9 to 12 cm H_2O. Contrast medium deposited in the choledochus before the exposure; in spite of this there is marked variation in the configuration:

a) Sphincter contracted, no filling of the intramural portion of the duct.

b) Slight relaxation of the sphincter with scanty filling of the intramural portion of the common duct and the pancreatic duct.

c) Further relaxation of the sphincter with more complete filling of the intramural portion of the common duct and reflux to the pancreatic duct.

d) Irregular, corkscrew-shaped, intramural portion of duct; reflux to the pancreatic duct.

e) to h) Continuous contrast flow with a hydrostatic pressure of 40 cm H_2O:

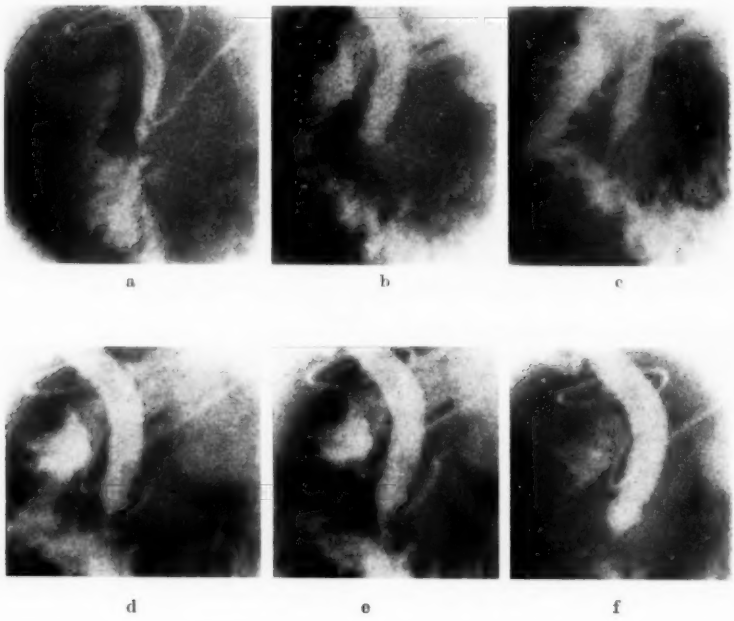
e) Narrow, almost closed intramural portion of duct.

f) Wide intramural portion, continuous reflux to the pancreatic duct.

g) and h) After morphia. Sphincter contracted but only small variations in appearance.

Comments. The choledochus in this case is moderately widened. The first four films demonstrate the variability without any infusion of contrast medium. Without other pressure variations than those caused by the respiration, the appearance of the terminal portion of the choledochus varies and, in certain sections, filling is also obtained of the intramural part and of the pancreatic duct. The intramural portion of the common bile duct at times has an irregular corkscrew-shaped appearance probably caused by contraction of the longitudinal muscle fibres of the sphincter complex. Under continuous infusion of contrast medium at comparatively high pressure an abundant flow of the medium to the intestine is obtained; this is, however, interrupted now and then by contractions of the sphincter muscles. The reflux to the pancreatic duct is more marked during this increased pressure. After injection of morphia the common channel is contracted and there is no reflux to the pancreatic duct.

Fig. 3. Case 2. For legend and comments, see opposite page.



Case 3 (Fig. 4). Female, aged 35, operated upon for primary chronic cholecystitis with calculus in the choledochus.

a) Flow pressure 14 cm H_2O. Choledochus slightly widened, flow of contrast medium to the intestine.

b) to e) Sudden increase in pressure in choledochus because the infusion pressure was raised to between 25 and 30 cm H_2O:
b) Choledochus considerably widened, sphincter contracted and no flow of contrast medium to the intestine.
c), d) and e) 6, 8 and 10 sec later, respectively. The sphincter successively relaxes, permitting an increasing flow of medium to the intestine and reflux to the pancreatic duct.

f) After injection of morphia (flow pressure unchanged at 25 to 30 cm H_2O). The sphincter is again contracted with scarcely any filling of the intramural portion of the common channel and no reflux to the pancreatic duct.

Comments. A sudden elevation of the pressure in the choledochus, induced by increased infusion pressure, provokes increased tone to the sphincter muscles, resulting in closing of the intramural portion and dilatation of the whole of the choledochus. With unchanged flow pressure, the sphincter spontaneously relaxes permitting an increasing flow of contrast medium to the intestine and the pancreatic duct. After injection of morphia there is a second and more marked increase in the tone of the sphincter.

a b c

d e

Case 4 (Fig. 5). Female, aged 61, operated upon for acute gangrenous cholecystitis. The contrast medium was continuously infused during the whole examination at a constant pressure of 23 cm H_2O.

a) and b) Sphincter contracted. In (b) the contrast-filled part of the choledochus has a concave termination, suggesting a concretion or tumour.

c) After administration of nitroglycerine, filling of the intramural portion of the choledochus and reflux to the pancreatic duct. Intestine widened and atonic.

d) and e) 10 and 12 min later, respectively. The effect of the nitroglycerine has disappeared and the spontaneous activity has returned.

Comments. In this case there is increased tone of the sphincter which remains contracted during the greater part of the first series. After administration of nitroglycerine the sphincter relaxes and the intramural section of the common duct is open. After the effect of the nitroglycerine has disappeared, the increased tone of the sphincter muscles returns spontaneously and the distal part of the choledochus again terminates abruptly. The pancreatic duct is also constricted distally. In a later phase the intramural portion of the choledochus becomes refilled at an unchanged flow pressure.

The abrupt and oblique termination of the choledochus resembles the appearance seen when a calculus or tumour is present in the terminal portion of the choledochus or the papillary region.

a b c d

Case 5 (Fig. 6). Female, aged 59. Cholecystectomy 15 years earlier and now operated upon for concretions in the choledochus. Choledochus considerably widened.

a) and b) Pressure of flow 8 cm H_2O: a) Sphincter contracted. Only slight filling of the intramural portion of the duct. b) Sphincter relaxed, permitting filling of the intramural portion of the duct. Flow of medium to the intestine.

c) and d) After injection of morphia: c) At a flow pressure of 10 cm H_2O. Concave termination of the choledochus as if caused by calculi or tumour. d) At a flow pressure of 30 cm H_2O. Flow through an extremely contracted sphincter.

Comments. The two first views of this case demonstrate spontaneous variation under constant flow pressure. After injection of morphia no filling of the intramural portion of the duct is obtained at a low flow pressure. The concave termination of the choledochus suggests a concretion or tumour but at an increased pressure this 'shape' has disappeared and a markedly contracted intramural portion of the duct is filled.

Discussion

Disturbances in the flow of bile and pancreatic juices may be caused either by organic changes such as tumours and strictures or by contractions of the sphincter muscles.

Contrast defects or deformation of the distal part of the choledochus and/or slow or no passage of contrast medium to the intestine are usually considered as a sign of calculi, tumour, or other organic lesion.

Our investigation demonstrates that the appearance of the terminal part of the choledochus is variable not only in different individuals but also in the same individual from one moment to another and depends on the tone of the sphincter muscle at the moment of exposure. This tone may be influenced by pressure variations and also by various drugs such as morphia. The varying configuration under constant infusion pressure depends on spontaneous contractions of the sphincter muscles.

Cholangiography performed in the conventional manner is unsatisfactory for functional studies inasmuch as it reproduces conditions at a

single instant — at the moment of exposure — in a phase where the tone of the sphincter and the injection pressure are not known.

Thus, no definite conclusions, either as regards the organic or functional conditions, can be drawn from the appearance of the choledocho-pancreatico-duodenal junction in separate views.

The conventional cholangiographic technique may give rise to functional changes in the tone of the sphincter muscles. A sudden increase in pressure in the choledochus caused by injection of contrast medium may thus provoke rapidly disappearing or more longstanding increase in the tone of the sphincter muscles which in turn may result in an abrupt or even slightly concave termination of the choledochus with a retarded flow of contrast medium to the intestine. This also applies in the case of premedication by morphia or derivatives of morphia which regularly give rise to a longstanding increase in the tone (8).

Roentgencinematography as described allows a more exact knowledge with differentiation between organic changes and those caused by functional variations in the configuration of the choledocho-duodenal junction. This is important from the therapeutic point of view as organic changes usually require continued surgical activity. In most of our cases, changes difficult to differentiate as functional or organic were seen at the conventional cholangiographic examination. It was possible by means of cinematography, however, to show in all cases that there were no organic changes but only variations of a functional nature in the configuration.

The method described, furthermore, allows physiologic studies of the function of the sphincter muscles under continuous recording of pressure and flow. It is possible also that continued studies may reveal functional disturbances at the choledocho-pancreatico-duodenal junction of importance as the cause of postoperative distress.

An interesting phenomenon is the reflux to the pancreatic duct observed in the films. It has been considered that reflux of bile from the choledochus to the pancreatic duct via a common channel may at least contribute to and constitute a factor in the probably complex etiology of acute pancreatitis.

Reflux to the pancreatic duct implies the presence of a common channel and a higher pressure in the choledochus than in the pancreatic duct. From this study it is seen that reflux occurs during certain phases in the dynamic variations, namely when the common channel is open and the most distal part of the sphincter contracted. It is also evident that the distal part of these ducts may close separately and, at least partly, independent of each other. Investigations in order to obtain a clearer conception of the reflux mechanism are proceeding.

SUMMARY

A method of roentgencinematographic cholangiography during continuous pressure-recording, permitting an exact study of the choledocho-pancreatico-duodenal junction is described. Thirty-four cases were examined. The relation between the flow pressure, the effect of a sudden elevation of the pressure in choledochus, and the administration of morphia and nitroglycerine is demonstrated. The importance of differentiating between configurations caused by organic changes and those produced by dynamic variabilities is emphasized.

ZUSAMMENFASSUNG

Eine röntgenkinematographische Cholangiographiemethode mit kontinuierlicher Druckregistrierung, welche ein genaues Studium des Verbindungsgebietes zwischen Choledochus, Pankreas und Duodenum gestattet, wird beschrieben. Vierunddreissig Fälle sind untersucht worden. Die Beziehungen zwischen dem Strömungsdruck, der Wirkung eines plötzlichen Anstieges des intracholedochalen Druckes und der Administrierung von Morphium und Nitroglyzerin werden aufgezeigt. Die Bedeutung der Differenzierung zwischen den Konfigurationen, welche durch organische Veränderungen bedingt sind, und solchen, die durch dynamische Schwankungen erzeugt sind, wird betont.

RÉSUMÉ

Description d'une méthode de cholangiographie radiocinématographique avec enregistrement continu de la pression, permettant une étude précise de la jonction cholédoco-pancréatico-duodénale. Trente-quatre cas ont été examinés. La relation entre la pression d'écoulement, l'effet d'une augmentation subite de la pression intracholédocienne, et l'administration de morphine et de nitroglycérine (trinitrine) est mise en évidence. Les auteurs insistent sur l'importance de la distinction entre les aspects dus à des modifications organiques et ceux dus à variations dynamiques.

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PRELIMINARY EXPERIENCES WITH PERORAL CHOLEGRAPHY

by

Georg-Fredrik Saltzman

When Schering A/G placed the intravenous contrast medium Biligrafin on the market in 1952 a new epoch was initiated in the roentgenology of the biliary tract. A method suitable for routine use in the examination of the bile ducts had become available.

It has always been generally possible to form some idea of the anatomy of the bile ducts by means of contrast media administered perorally, to the extent that the cystic duct and the common bile duct may be more or less well filled in up to 80 % of all cases, when the gallbladder empties after a fatty meal. Ever since 1949, when the tri-iodized contrast media began to be used for peroral cholecystography, the bile ducts have occasionally been visible as early as the filling phase of the gallbladder although it has seldom been possible satisfactorily to assess their condition. The main reason for this is that the films of the bile duct region were usually not obtained until about 12 hours after the patient had taken the contrast medium. HOLMDAHL & LODIN demonstrated that the concentration in the blood of perorally administered tri-iodized contrast medium in the form of iopanoic acid and its sodium salt (Bilijodon and Bilijodon-Natrium (Leo), respectively) is at its highest 4 to 6 hours after the patient

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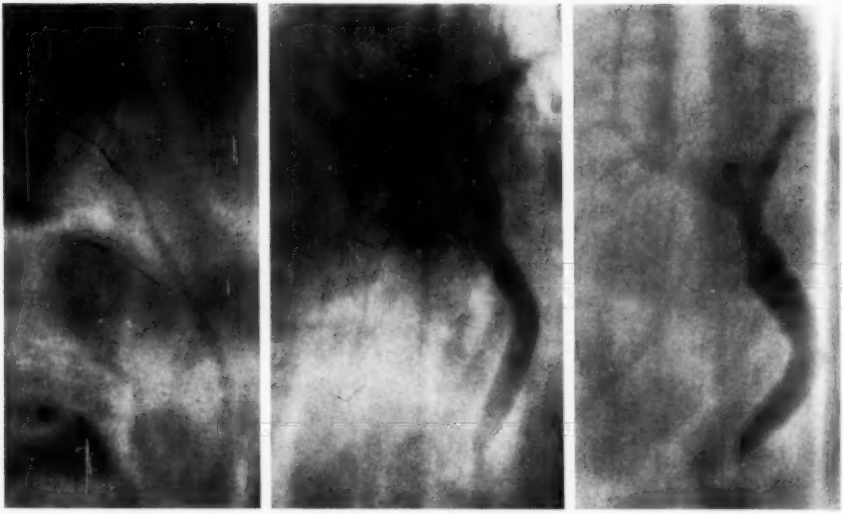
Fig. 1. Satisfactory filling of the bile ducts 5 hours after 4 g Bilijodon-Natrium in capsule form.

has swallowed the medium. We consequently obtained a series of films in a few cases 4 to 8 hours after the administration of Bilijodon-Natrium tablets, and in some instances secured a filling of the bile ducts which was quite satisfactory for diagnostic purposes (Fig. 1). This is by no means always the case, however, and the method is consequently not suitable for routine work.

GUNNARSON towards the end of 1958 presented the first report on a serviceable method for peroral cholegraphy. An important feature of the technique was the introduction of the sodium salt of iopanoic acid, which had proved to be more readily absorbed from the intestine than iopanoic acid as such (HOLMDAHL & LODIN). It was demonstrated in preliminary investigations by GUNNARSON that an aqueous solution of Bilijodon-Natrium, administered directly into the duodenum through a catheter, gave a contrast density superior to that obtained at a comparative examination with intravenous cholegraphy (Biligrafin). The method is naturally not practicable for routine work, but it affords some indication of the goal to be aimed at, namely the introduction of the whole dose of contrast medium at one time into the small intestine, i. e. the site where the medium is absorbed.

The pharmaceutic firm of AB Leo has for some time been engaged in trial manufacture of gelatine capsules containing Bilijodon-Natrium dissolved in distilled water. The concentrated 50 % solution is supplied in capsules of two sizes, containing 0.7 and 0.45 g of contrast medium, respectively. The dose recommended in the beginning was 0.7 g per 10 kg bodyweight but this was later fixed at 0.45 g/10 kg.

In a preliminary series of cases examined with Bilijodon-Natrium in gelatine capsules, GUNNARSON obtained good contrast filling of the bile ducts in 80 % of cases. In 38 cases the results obtained with Bilijodon-Natrium capsules were compared with those achieved after the intravenous administration of Biligrafin in the same cases. On an average, the



a b c

Fig. 2. a) Normal bile ducts. b) and c) Dilated bile ducts without concretions in patients who had undergone cholecystectomy.

peroral method gave slightly better filling but the difference was not great. It should, however, be mentioned that the intravenous method proved to be superior in a number of cases. Only such cases as received the original, higher dose of contrast medium seem to have been used in this material.

We have had an opportunity, through the courtesy of AB Leo, of carrying out cholegraphic examinations with Bilijodon-Natrium capsules during the past few months. Seventy examinations have been made up to the present. As our experiences differ in some respects from those of GUNNARSON a short report seems to be justified.

The majority of our patients (57) received 4.2 to 4.5 g of contrast medium, in other words a dose of approximately the same size as the higher dose recommended by Leo. The capsules were given with a glass of distilled water and the patient was directed to lie on his right side till the contrast medium had left the stomach. Despite their size, the capsules seem to be easy to swallow; only one of our patients had difficulties in this respect. The capsules should not be crunched in the mouth as the contrast medium has a very unpleasant taste.

The gelatine capsules dissolve in the stomach. From the viewpoint of the diagnosis, it would be advantageous if the whole dose of contrast medium could be rapidly transported to the small intestine so that it

could be absorbed within a short period. This occurs in patients who have undergone resection of the stomach, at least in those treated by the Billroth II operation; in these cases the medium is visible in the bile ducts 15 to 20 minutes after medication, and optimal contrast density is obtained approximately one hour later. In one of our 5 cases treated by a Billroth II stomach resection there was sufficient contrast medium in the gallbladder plainly to demonstrate three fairly large cholesterin concretions as early as 5 minutes after the patient had swallowed the Bilijodon-Natrium capsules. In all the patients with a stomach resection the contrast medium had almost completely disappeared from the bile ducts after 2 hours.

In the majority of the patients with a stomach which was roentgenologically or clinically normal, the time from the administration of the contrast medium to the occurrence of optimal contrast density in the bile ducts showed great variation. In a few cases the time required was 2 to 3 hours while in most of them it was between 4 and 7 hours. The decisive factor here seems to be the time taken for the greater part of the contrast medium to leave the stomach. In an attempt to accelerate the evacuation of the stomach by dilating the pylorus we gave a few patients 5 drops of Eumydrin sublingually, but no appreciable effect could be noted.

A diagnostically satisfactory concentration of contrast medium in the bile ducts was obtained in most of our cases. Fig. 2 shows the roentgen films from a few peroral cholegraphies. The concentration of the medium exhibited great variation in the individual cases, however. It was revealed very plainly in our series that the rapidity with which the contrast medium passed from the stomach into the small intestine was of decisive significance. Those patients in whom the medium remained for a long period in the stomach and then passed only slowly into the duodenum all had a lower concentration of contrast medium in the bile ducts than those in whom the transportation of the medium through the pylorus had taken place rapidly. We made use of tomography both in the intravenous and peroral cholegraphies in order to improve the possibilities of satisfactory interpretation. When it seemed as if optimal contrast density would soon be reached in the bile ducts the patients were given a small dose of morphia subcutaneously; this caused contraction of the sphincter of Oddi and consequently stagnation of the contrast-bearing bile in the ducts. As far as we could judge, this measure in the majority of cases increased the contrast density in the ducts.

With this dose of 4 to 5 g Bilijodon-Natrium in capsule form more than half the patients (35 out of 57 cases) had mild reactions in the form of nausea and diarrhoea. Nausea was recorded in 23 cases, and in 6 of these it was combined with vomiting; in one of the latter, roentgen control

revealed that the patient had lost all the contrast medium by vomiting. Twenty-two patients had diarrhoea; strangely enough, the diarrhoea often began as early as 15 minutes after the patient had swallowed the capsules, in other words, before any appreciable amount of contrast medium had had time to travel beyond the pylorus. Ten patients had both nausea and diarrhoea. The incidence of diarrhoea would probably have been much higher if we had not given 10 drops of tincture of opium at the same time as the contrast capsules in the last 17 examinations. Only 2 of the latter 17 patients had diarrhoea; the incidence of nausea, on the other hand, was not affected by the opium medication. Owing to the fact that we did not correlate the dose with the bodyweight (which was nevertheless recorded) in the 57 cases which received the higher dose of contrast medium, but used instead a standard dosage (0.45 g × 10 or 0.7 g × 6), we were able to note considerable variations in the individual tolerances. Whereas some patients had diarrhoea and/or nausea after a dose of 0.45 g per 10 kg bodyweight, others showed no reactions at all to 1 g per 10 kg bodyweight. This applies to patients not given opium. Our material furnished no conclusive information as to whether the dose of contrast medium should be adjusted according to bodyweight or whether in general a dose of 4 to 5 g can be used. Our impression is that, in practice, the latter simplified form of dosage will give completely satisfactory results.

Fig. 3. Peroral cholegraphy with Bilijodon-Natrium capsules. Concretions in normally wide bile ducts and in the gallbladder.

In only one case were side-effects of a more dramatic nature observed. In this patient urticaria and high fever as well as slight mental confusion were noted 10 hours after the administration of the contrast medium. The signs disappeared completely after a few hours.

In 13 cases we used the lower dose of Bilijodon-Natrium recommended by AB Leo, namely 0.45 g per 10 kg bodyweight. Mild diarrhoea was noted in 3 of these cases, in 2 of them combined with nausea. These 13 cases did not receive opium. The material is too small for definite conclusions to be drawn, but it looks as if a higher dose of contrast medium produces more marked reactions.

It was obvious, however, that the lower dose did not give satisfactory contrast density in the bile ducts. The concentration of the medium in the bile ducts was hardly ever as high as that obtained with the larger dose, and in many cases it was unsatisfactory from the diagnostic standpoint.

In those cases in which the gallbladder was intact and visible in the roentgen films, diagnostically satisfactory density was obtained simultaneously with, or shortly after the occurrence of optimal density in the bile ducts. In a few instances in which the higher dose was used films were taken as late as 12 hours after the administration of the medium. The contrast-filling of the gallbladder in a few cases was then so dense that small concretions could easily have been concealed. By applying strong compression we considered, however, that we had eliminated this disadvantage. In no case did we observe any troublesome layer formation between contrast-bearing and non-contrast-bearing bile.

Conclusions

Peroral cholegraphy with Bilijodon-Natrium is in all essentials as good a method for the examination of the bile ducts as intravenous cholegraphy with Biligrafin. The dose should amount to 4 to 5 g. Nausea and fairly severe diarrhoea often arise after this dose, but diarrhoea can be kept under control if the patient is given 10 drops of tincture of opium with the capsules. Other reactions seldom occur.

Peroral cholegraphy forms an interesting complement to earlier roentgen methods for the examination of the bile ducts. It is our belief that it may be used to advantage in those cases in which a test injection previous to intravenous cholegraphy has revealed evidence of hypersensitivity. We have used peroral cholegraphy in 2 patients in whom urticaria arose after a test injection for the intravenous method and no troublesome reactions occurred. According to GUNNARSON, the contrast density in the bile ducts obtained with peroral cholegraphy is in some cases superior to that afforded by the intravenous method. Although we have not encountered any case in confirmation of this, GUNNARSON's observations would seem to suggest that an intravenous cholegraphic examination not producing satisfactory contrast density in the bile ducts might be supplemented by an examination with the peroral method.

There are, however, still many reasons for hesitation in suggesting that peroral cholegraphy might be used to replace the intravenous form as the method of choice for bile duct examinations. Because of the long, variable interval elapsing between the administration of the contrast medium and the optimal filling of the ducts the peroral examination

places a heavier burden on a busy roentgen department than the intravenous method.

The use of peroral cholegraphy as a routine method might, however, be justified in those cases in which the gallbladder has not been removed. The examination would then be used as a substitute for both peroral cholecystography and intravenous cholegraphy. As a matter of fact the intravenous method not infrequently causes such confusing layer formation between contrast-bearing and non-contrast-bearing bile in the gallbladder that it is often necessary to carry out a special examination of this organ with the peroral administration of contrast medium.

Since one of the essentials for a good diagnostic result is that as large an amount of contrast medium as possible should be absorbed within the shortest possible time, the usefulness of the method would be considerably increased if the contrast medium could be more rapidly transported intact to the small intestine where it is absorbed. It would be of great practical value to be able to determine with more accuracy than is possible at present the exact time when the absorption of the contrast medium takes place.

SUMMARY

Preliminary experiences with peroral cholegraphy carried out with Bilijodon-Natrium (Leo) are reported. Technical aspects of the examination are discussed at some length. Side-effects are described and suggestions advanced for their reduction. The advantages and disadvantages of the method, as well as its comparison with intravenous cholegraphy, are presented.

ZUSAMMENFASSUNG

Vorläufige Erfahrungen mit der peroralen Cholegraphie mit Bilijodon-Natrium (Leo) werden mitgeteilt. Technische Aspekte der Untersuchung werden ziemlich eingehend besprochen. Nebenwirkungen werden beschrieben und Vorschläge, jene zu verringern, werden gemacht. Die Vor- und Nachteile der Methode sowie ein Vergleich derselben mit der intravenösen Cholegraphie werden vorgelegt.

RÉSUMÉ

L'auteur présente une expérimentation préliminaire de cholégraphie par voie orale au moyen de Bilijodon-Natrium (Leo). Il étudie assez longuement les aspects techniques de cet examen. Il décrit les effets secondaires et propose des moyens de les diminuer. Il expose les avantages et les inconvénients de cette méthode et la compare à la cholégraphie intraveineuse.

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ORAL CHOLEGRAPHY

by

Eric Gunnarson

The availability of tri-iodized contrast media (Telepaque, Teridax, Vesipaque) has improved the possibilities of demonstrating the condition of the biliary tract. In cases in which no filling of the gallbladder is obtained, a faint filling of the biliary ducts may, however, sometimes be observed, as occurred in about 27 % of our cases studied with Telepaque. Though such findings do not permit a positive diagnosis, they do show that the contrast medium has been absorbed and excreted by the liver and that the absence of filling is due to disease of the gallbladder.

Clinical cholegraphy was made possible by the introduction of Biligrafin for intravenous use in 1953. Intravenous injection is, however, less acceptable to the patient than oral administration and sometimes causes allergic reactions (THEANDER 1955). TWISS, GILETTE, BERANBAUM et coll. (1955) therefore tried large doses of Telepaque tablets and gave a total dose of 6 g Telepaque administered in fractions at varying intervals. Seven to twelve hours after the last fraction of the dose, faint filling was obtained of the bile ducts in 74 out of 106 patients who had undergone cholecystectomy. STAMATAKOS and TABER (1957) tried the method in cases in which cholecystography had produced no filling of the gall-

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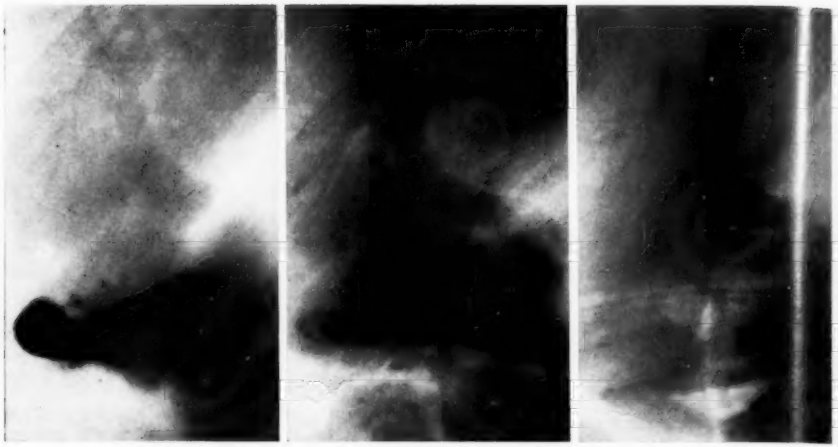
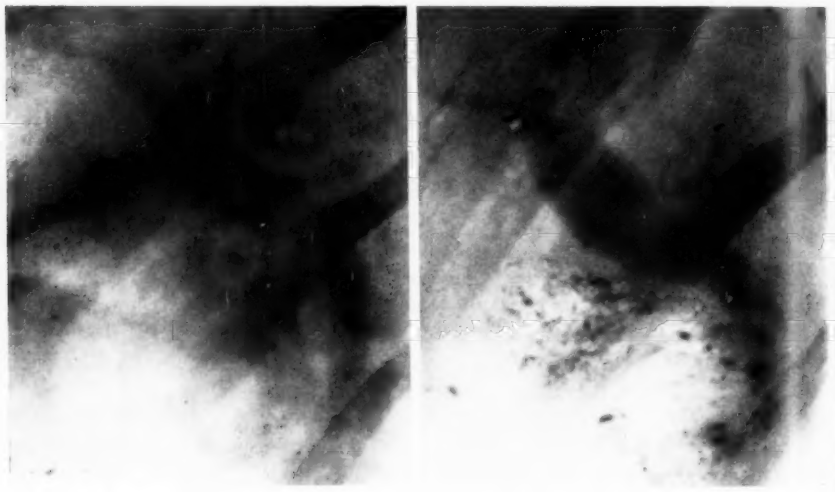


a b c

Fig. 1. Oral cholegraphy. a) 15 minutes after swallowing capsules: contrast medium in pyloric antrum and canal as well as in duodenum, bile ducts beginning to appear. b) After further 30 minutes: good filling of bile ducts. c) Intravenous cholegraphy of same patient.



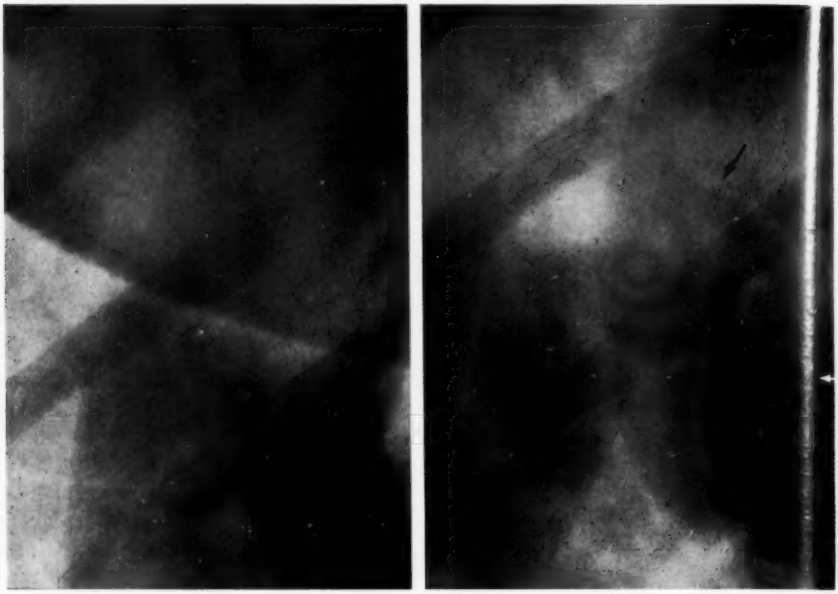
a b

Fig. 2. Intravenous and oral cholegraphy in same patient as in fig. 1. a) 45 minutes after injection of 20 ml Biligrafin-forte. b) 50 minutes after ingestion of 4.5 g Bilijodon-Natrium in capsules.

bl dder. The patients received a total dose of 6 g administered in fractio s of 1 g every other hour; the biliary ducts were faintly outlined in 48 of 67 patients examined in this way. It is clear that such examinations ar much more time-consuming than intravenous cholegraphy with Biligr fin and that the concentration of contrast medium obtained in the bil ducts is often much lower. The contrast media used consist of derivativ s of phenyl-substituted fatty acids of fairly low solubility and, as is ap arent from the common occurrence of residual contrast medium in th digestive tract, these are not readily absorbed. RENCK (1954) found res dues, sufficiently large to interfere with the examination, in the dig stive tract in 53 % of all patients who had received Telepaque in a tot l dose of 3 g.

In 1955 we began to use the sodium salt of iopanoic acid, Bilijodon-Na rium, and found that appreciable residues occurred in the intestines in only 13 % of the cases after a dose of 4 g (PETERHOFF 1956). In addition, the bile ducts were faintly defined in as many as 50 % of cases in which no filling was obtained of the gallbladder, as against only 27 % of cases examined with Telepaque. The decrease in the occurrence of residual contrast medium in the intestine and the increase in the frequency with which a filling was obtained of the bile ducts show that the sodium salt, due to its higher solubility, is more readily absorbed than the uncombined acid. Iopanoic acid may, however, be formed and precipitated in the stomach by reaction between Bilijodon-Natrium and the hydrochloric acid present in this organ. The iopanoic acid is then in an amorphous form, however, and lies over a large contact area, which facilitates its dissolution and absorption. For effective and rapid absorption the contrast medium should reach the intestine in solution. Bilijodon-Natrium is readily soluble in water and other solvents, such as certain alcohols. Preliminary trials showed that Bilijodon-Natrium gives a quicker and better filling of the bile ducts when administered orally as an aqueous solution than when the contrast medium is taken as tablets. A dose of 4 g dissolved in distilled water outlined the biliary tract within, on the average (21 cases), 45 minutes, while the concentration of contrast medium in the bile ducts after the same dose given in tablets was lower and did not reach a maximum until after 2 to 3 hours (80 cases). This advantage of the aqueous solution is, however, considerably reduced by the fact that it produces a most disagreeable sensation of burning in the mouth and throat.

In an attempt to study the common bile duct and the duodenum simultaneously the contrast medium was deposited directly into the duodenum, twenty subjects receiving 4 g Bilijodon-Natrium in water through a duodenal tube. The contrast medium was regularly absorbed and the bile ducts were all outlined within 20 to 30 minutes. The method, although useful for studying the rate of absorption of the contrast medium from the small intestine, is hardly suitable for routine clinical use.



a b

Fig. 3. Intravenous and oral cholegraphy in same patient as in figs. 1 and 2. a) Intravenous: no filling of bile ducts despite repeated attempts. b) Oral: moderate filling.

In an endeavour to secure a method for everyday oral cholegraphy a gelatine capsule containing 0.45 g Bilijodon-Natrium dissolved in polyvalent alcohols was prepared in co-operation with the Research Department of AB Leo, Sweden; a wetting agent, Tween 80, was incorporated to accelerate absorption. Water could not have been used as a solvent as it would have dissolved the capsules. The capsules contain a 50 % solution of contrast medium and are therefore heavier than the gastric juice and, if the patient is directed to lie on his right side as soon as he has swallowed them, they sink towards the pylorus and dissolve. The contrast medium is in this way administered in solution without producing any disagreeable taste and rapidly reaches the small intestine without any reaction with the gastric juice (Fig. 1).

In practice we use the following method: After ingestion of one capsule of 0.45 g Bilijodon-Natrium per 10 kg bodyweight, washed down with a large glass of distilled water (about 300 ml), the patient lies on his right side for at least 60 minutes; by this time the contrast medium will usually have been absorbed and reached a satisfactory concentration in the bile

a b

Fig. 4. Oral cholegraphy in patient with post-operative biliary dyskinesia. a) 50 minutes after ingestion of Bilijodon-Natrium in capsules, morphia 0.3 cg given subcutaneously. b) 20 minutes after injection of morphia: pain developed in right side of abdomen, good filling of bile ducts, common bile duct considerably widened.

ducts. Films are then taken. If any contrast medium should still be present in the stomach, the patient is given another large glass of distilled water to drink, and a further film is obtained 30 minutes later. Only 'cup-and-spill' stomachs will as a rule then contain any contrast medium. If morphia is to be injected to increase the amount of contrast medium in the intrahepatic bile ducts or for any other purpose, the examiner should always be sure that no contrast medium remains in the stomach. Morphia causes contraction of both the sphincter of Oddi and the pylorus and therefore prevents the passage of the contrast medium into the intestine (Fig. 4).

Like oral cholecystography with tablets, the ingestion of Bilijodon-Natrium in capsules was sometimes followed by nausea and diarrhoea. These reactions were more common after the ingestion of capsules, but were never serious. The material is not yet large enough to permit any valid conclusions about other possible side-reactions.

One hundred and sixteen ambulatory patients, aged 20 to 45 years, referred for routine roentgen examination of the hepatobiliary tract were selected at random for the present investigation. Of these, 96 received the contrast medium in capsules and 20 by the duodenal tube. A total of 58 of the patients were re-examined on later occasions with 20 ml Biligrafin-forte administered intravenously. The results obtained following the oral administration are given in Table 1.

Table 1

Oral cholecystography of the cholecystectomized (101) and non-cholecystectomized (15) patients	Good definition of bile ducts	Faint definition of bile ducts	No definition of bile ducts
116	80	22	5

In Table 2 a comparison is made of the results obtained in the 58 patients examined by both methods.

Table 2

Patients examined with capsules and with Biligrafin-forte	Oral cholegraphy better	Intravenous cholegraphy better	No difference
38	17	8	13
Patients examined with intraduodenal deposition of Bilijodon-Natrium in solution and Biligrafin-forte			
20	17	2	1

Oral cholegraphy was satisfactory in 7 cases in which the intravenous method had failed, while intravenous cholegraphy proved successful in 2 cases in which the oral method had failed.

Discussion

Filling of the bile ducts was found to be equally good, if not better, after the oral administration of Bilijodon-Natrium in solution as after the intravenous injection of Biligrafin-forte. An advantage of the oral method is that satisfactory filling of the bile ducts is sometimes obtained in cases in which the concentration of the contrast medium in the ducts following intravenous injection is not sufficient to permit a positive

diagnosis (Fig. 3). This may be explained by the assumption that after absorption the bulk of the contrast medium administered by the oral route is initially present only in the portal circulation. If the flow to the liver is not occluded the contrast medium is transported through the portal vessels to the liver and then through the bile ducts back to the intestine where part of it is reabsorbed.

HOLMDAHL and LODIN (1959) studied the concentration of iodine in serum from the general circulation after cholecystography with Bilijodon-Natrium and found that it did not reach a maximum until after 4 to 6 hours and that it was rather low during the first 2 hours. In the preliminary trial with Bilijodon-Natrium tablets in the present investigation, however, the filling of the bile ducts reached an optimum within 2 to 3 hours. This shows that Bilijodon-natrium is absorbed and excreted more rapidly than indicated by the blood concentration curve.

Biligrafin on injection is distributed in the general circulation before it is excreted via the liver and kidneys. Furthermore, Biligrafin can only pass through the liver once since it cannot be absorbed from the intestine.

A degree of filling to permit of a positive diagnosis is, as mentioned, sometimes obtained only by one of the methods. The availability of the oral method has therefore increased the possibility of obtaining satisfactory outlining of the bile ducts.

SUMMARY

A new method of oral cholegraphy with a 50 % solution of the sodium salt of iopanoic acid (Bilijodon-Natrium) in gelatine capsules is described. The results were comparable to those obtained following the intravenous injection of Biligrafin-forte. Filling was obtained by the oral method in some cases in which the intravenous procedure failed and vice versa.

ZUSAMMENFASSUNG

Eine neue orale Cholegraphiemethode mit 50%iger Lösung des Natriumsalzes der iopanoischen Säure (Bilijodon-Natrium) in Gelatinekapseln wird beschrieben. Die Ergebnisse werden mit den nach intravenöser Injektion von Biligrafin-forte erhaltenen verglichen. Füllung wurde mit der oralen Methode in einigen Fällen erreicht, in welchen die intravenöse Prozedur fehlschlug: im gleichen Masse ergab sich auch das umgekehrte Verhältnis.

RÉSUMÉ

L'auteur décrit une nouvelle méthode de cholégraphie orale au moyen de capsules de gélatine contenant une solution à 50 % du sel de sodium de l'acide iopanoïque (Bilijodon-Natrium). Les résultats ont été comparables à ceux obtenus après injection intraveineuse de Biligrafin-forte. L'opacification a été obtenue par la méthode orale dans certains cas où la méthode intraveineuse avait échoué, et vice versa.

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CONTRAST MEDIUM PRECIPITATE IN THE HUMAN GALLBLADDER

by

Georg Theander

Precipitation of contrast medium in the human gallbladder is almost unknown. It was observed at cholecystography with iopanoic acid (Telepaque) in a woman with several small gallbladder stones, some of which became enclosed by a transient mass of varying shape (THEANDER 1955). It might also have caused the inconstant opaque coating of individual stones in the gallbladder or common bile duct found by SALZMAN et coll. (1958) in a few cases after prolonged treatment with Telepaque and referred to by them as the 'rim sign'. No further observations of the phenomenon seem to be on record.

In the present paper a report is given of 8 cases of the precipitation of contrast medium in the gallbladder after the administration of the sodium salt of iopanoic acid — (Bilijodon-Natrium Leo) — in the following abbreviated to Bi-Na. An attempt is also made to collect significant data in a systematic survey of the condition. Though necessarily tentative owing to the incompleteness of the material available, such a review appears to be desirable for further investigation of the phenomenon.

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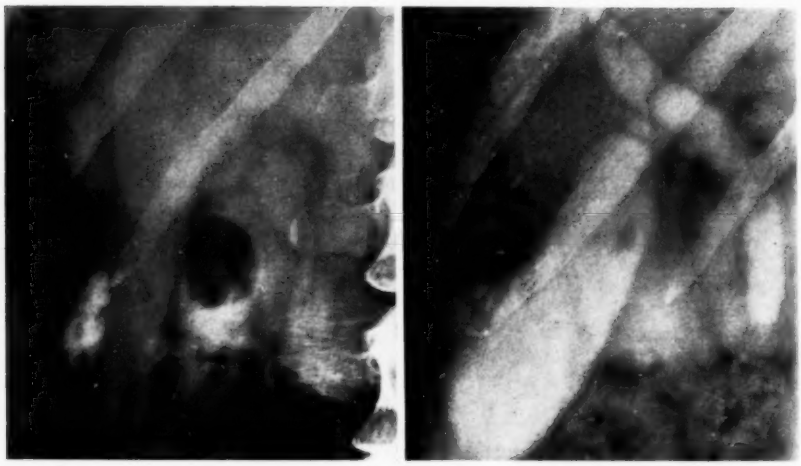

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Fig. 1. Case 1. a) After 6 g Bi-Na. Mass apparently enclosing stones in gallbladder. b) Cholecystography 2 months later. Slightly widened ducts but otherwise normal finding.

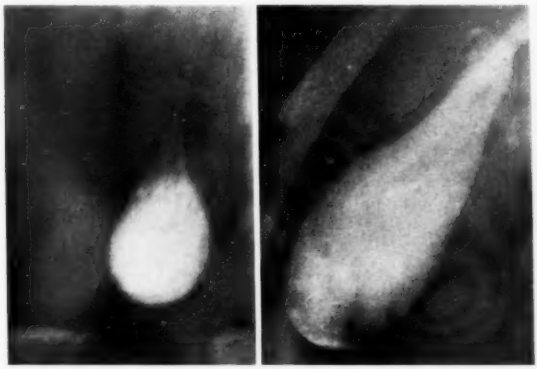
Case reports

Case 1. Woman, aged 50, was referred for cholecystography because of abdominal pain, presumedly biliary in origin. She was given 3 g Bi-Na, the dose being repeated the next day. Upon examination the day after the second dose an irregular, well defined mass, about 22 × 10 mm, was seen in the right hypochondrium, apparently outside the alimentary tract and probably in the gallbladder. It enclosed some rounded formations resembling small calculi (Fig. 1a). Cholegraphy with Biligrafin-forte was performed seven weeks later after the pain had subsided. The mass was no longer seen and the biliary system appeared normal, except that the large ducts were somewhat wide (Fig. 1b). The position of the gallbladder suggested that the mass previously observed had been situated within it.

On re-examination with Bi-Na about 20 months later the appearances were normal. A dose of 6 g of the contrast medium was given, fractionated as before, but this time without obvious precipitation in the gallbladder. The patient has since been symptom-free.

Case 2. Woman, aged 26, referred for cholecystography for vague abdominal pain of about a year's duration. Bi-Na was given in doses of 3 g on 2 consecutive evenings and films were obtained in the morning after each dose. On both occasions the gallbladder was satisfactorily filled and found to contain a large number of minute stones. No precipitate of contrast medium could be demonstrated the first day (Fig. 2a), but on the second day a thin layer of precipitate adhered to the fundus of the gallbladder (Fig. 2b); it was dispersed in the fluid contents of the gallbladder on repeated changes in posture. On examination 5 days later without further administration of contrast medium the gallbladder was no longer visible nor was there evidence of any residue of the precipitate.

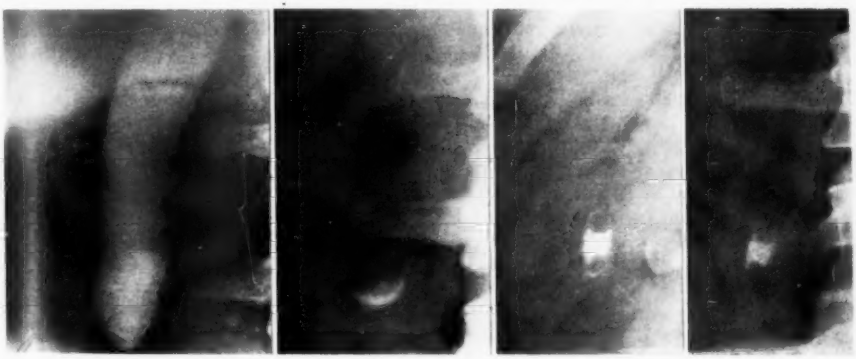
Cholecystography with Bilitrast after another 3 days confirmed the presence of stones, but no precipitation of contrast medium was seen on that occasion. At cholecystectomy, 6 months later, the gallbladder contained numerous small stones, but was otherwise of normal gross appearance.



a b

Fig. 2. Case 2. Cholecystography after a) 3 g, b) 6 g Bi-Na. Precipitate adherent to fundus in recumbent position (b).

Case 3. Woman, aged 38, with a history of repeated attacks of biliary colic; cholecystography 3 years previously had revealed some small gallbladder stones (Fig. 3a). Bi-Na administered in doses of 3 g failed to demonstrate the gallbladder, but a small amount of some very opaque material was observed in the right upper quadrant of the abdomen, presumably in the gallbladder. This substance did not seem to vary in amount from the one day to another, but it did change in shape. Thus on the first day it seemed to form a somewhat irregular layer adherent to the fundus of the gallbladder (Fig. 3b), while on the following day it appeared as an oblong and somewhat heterogeneous mass apparently situated longitudinally in the gallbladder; it was unchanged by posture and enclosed a clear rounded region at each pole (Fig. 3c and d). The mass was still present a fortnight later when the patient was examined without further administration of contrast medium; it was then of the same shape and size as when first observed.



a b c d

Fig. 3. Case 3. a) Floating stones. b) Three years later, after 3 g Bi-Na. Gallbladder not filled but precipitate at fundus in prone position. c) and d) Prone and erect respectively, after further 3 g Bi-Na. Precipitate, changed in shape but not appreciably in amount, apparently enclosing stones.

Fig. 4

Fig. 5 a

Fig. 5 b

Fig. 4. Case 4. Stones and precipitate after 6 g Bi-Na.

Fig. 5. Case 5. a) Cholecystography, 6 g Bi-Na. Recumbent. Gallbladder not filled but precipitate adherent to fundus. b) Normal cholegraphy.

The patient was re-examined 7 months later on admission for cholecystectomy. Films taken before the administration of contrast medium did not show any residue of the mass previously observed. In order to obtain a specimen of precipitate from the gallbladder for chemical analysis, the patient was given 6 g Bi-Na the day before the operation. No demonstrable precipitate was, however, obtained. As previously, no filling of the gallbladder was obtained. At operation the gallbladder was found to contain concretions corresponding in size to the clear formations previously observed in the precipitate. No iodine was demonstrable on chemical analysis of its fluid content. Centrifugation of the gallbladder bile produced an extremely small sediment which contained 0.8 mg calcium but no iodine.

Case 4. Woman, aged 61, with vague abdominal symptoms. Demonstration of the gallbladder was unsuccessful after 3 g Bi-Na and only poor after an additional dose of 3 g. At both examinations, however, the fundus of the gallbladder was occupied by a mass containing several clear formations of different sizes (Fig. 4). The latter moved with a change in posture of patient whereas the mass at first persisted in the fundus but disappeared on repeated change in posture. The size of the mass did not vary appreciably at the examinations.

At follow-up examination a week later without further administration of contrast medium neither the gallbladder nor any residue of the mass was visible. The patient refused cholecystectomy.

Case 5. Woman, aged 40, with a history of typical biliary colic and periods of jaundice. Cholecystography was performed shortly after such an attack; Bi-Na was given in doses of 3 g on 2 consecutive evenings and films were obtained in the morning after each dose. The gallbladder was not filled but on both days the films revealed a mass apparently

a b c

Fig. 6. Case 6. a) Prone, b) Erect, c) Right lateral. After 6 g Bi-Na. Precipitate in irregular layer between a heavy clear and a lighter opaque fraction of gallbladder contents.

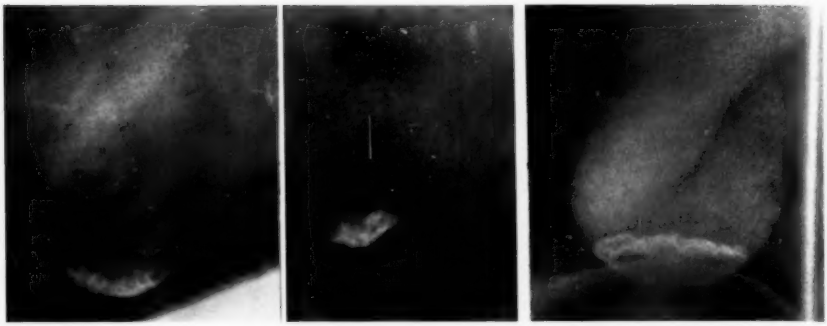
outlining part of the fundus of the gallbladder (Fig. 5a). The opacity did not seem to vary in size at the two examinations but on repeated change in posture it gradually disappeared.

On follow-up examination 5 days later without further administration of contrast medium the findings were essentially the same as before. Three months later, however, the mass was no longer visible. Cholecystography with 6 g Bi-Na was repeated after a further three months and again four months later. On both occasions the gallbladder was well filled without demonstrable precipitate or stones; cholegraphy with Biligrafin-forte after the first of these cholecystographies showed that the bile ducts were also normal in appearance (Fig. 5b).

Case 6. Woman, aged 78, being cared for in hospital for arterial hypertension, weakness after right-sided hemiplegia, and senility, developed obscure abdominal symptoms possibly biliary in origin. Cholecystography was performed. The gallbladder was not satisfactorily demonstrated with 3 g Bi-Na and an additional dose of 3 g was therefore given. Demonstration of the gallbladder was only slightly better on the following day, but a horizontal opaque layer was now seen in the gallbladder above a clear fraction of its contents. The clear fraction remained below the horizontal layer on change in posture (Fig. 6).

On follow-up examination a week later without further contrast medium the gallbladder was no longer visible. No definite change had occurred in the amount of the opaque material present but the clear fraction had disappeared. The lowermost part of the gallbladder now contained the precipitate, which was heterogeneous in density and enclosed numerous small clear areas (Fig. 7a). Further examination 10 days later revealed a decrease in the amount of the opaque substance, which now formed an irregular mass at the bottom of the gallbladder. The clear formations in the mass were now not so distinct as before (Fig. 7b).

Essentially the same finding was obtained on examination more than one month after the administration of the contrast medium, but three months after this the mass was no longer demonstrable and cholegraphy was normal. On re-examination with Bi-Na at this time, the same sequence of events was observed as previously. Thus, demonstration of the gallbladder required 6 g Bi-Na, divided over 2 consecutive days, and precipitation of the contrast medium did not occur until after the second dose. It was then present in about the same amount as on the previous occasions. For a few days the gallbladder content was then made up of three separate fractions of different opacity (Fig. 7c).



a b c

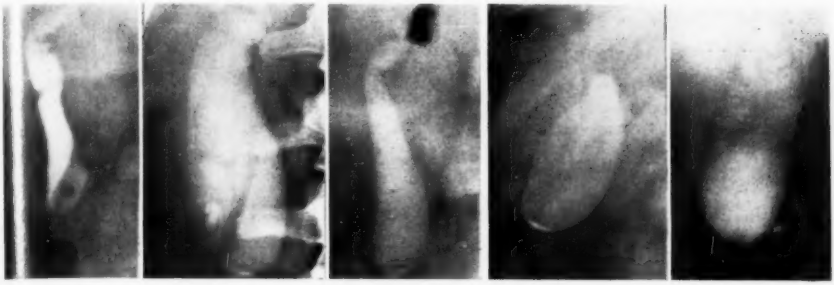
Fig. 7. Case 6. a) A week later than in fig. 6. Erect. The clear layer has disappeared. Precipitate at fundus, apparently enclosing stones. b) Ten days later. Residues of precipitate. c) Three months later. After 6 g Bi-Na apparently same amount of precipitate as in fig. 6. Layer formation.

Bi-Na was again administered three months later in doses of 3 g on two successive evenings. Films obtained in the morning after each dose did not reveal any precipitate or fractionation, but on the following day a horizontal opaque layer again appeared above a clear portion of the gallbladder's contents. The amount of the precipitate appeared to be about the same as that initially observed on the previous occasions. The patient's poor condition contra-indicated cholecystectomy.

Case 7. Woman, aged 29, with a history of recurrent obscure abdominal symptoms. On cholecystography (6 g Bi-Na) the gallbladder filled satisfactorily; a pea-sized clear region, probably representing a stone, was noted but no precipitate was observed (Fig. 8a). Because of marked eccentric contractions of the gallbladder at this examination the patient was re-examined 2 days later after the administration of 6 g Pheniodol (Bilitrast). As expected (ANDRÉN & THEANDER 1958) the gallbladder, being normally filled, was then larger, and eccentric contractions did not occur, but a small amount of a very opaque material was now present within the lumen. It first lay at the fundus (Fig. 8b), but on change in posture it was dislodged and disappeared. Three grams of Bi-Na were given the same day but probably eliminated by subsequent vomiting. Films obtained on the following day revealed roughly the same amount of precipitate as previously, outlining the fundus of the gallbladder; in the erect position the concretion was seen to lie upon the precipitate (Fig. 8c). The patient refused cholecystectomy.

Case 8. Woman, aged 55, who had had a normal cholecystography seven years previously, was now again referred for a similar examination following an attack of colic, apparently biliary in nature. The gallbladder was filled after Bi-Na in doses of 3 g on two consecutive days; there was a pea-sized stone in the gallbladder together with a small amount of an opaque dispersible mass.

Re-examination a week later after the administration of 3 g Bi-Na on each of the two preceding days gave a similar result. The opaque mass, apparently unaltered in size, first formed a thin layer adherent to the fundus of the gallbladder, whereas the concretion moved with change in posture; after the patient had been turned several times, however, the mass temporarily vanished (Fig. 9). Six days later it had definitively disappeared and the gallbladder was no longer demonstrable. Cholecystography with Bi-Na two weeks after this showed the same sequence of events. The patient refused cholecystectomy.



a b c

Fig. 8. Case 7. a) Eccentric contractions after 6 g Bi-Na. Stone in gallbladder but no precipitate. b) and c) Recumbent and erect, respectively. Precipitate at fundus after further 6 g Bilitrast. In (c) the stone lies upon the precipitate.

a b

Fig. 9. Case 8. Stone and precipitate after 6 g Bi-Na. a) Recumbent position, and b) erect. The precipitate initially adhered to fundus but disappeared with repeated change in posture (b).

Discussion

In all these cases, as in the one previously described (THEANDER 1955), the diagnosis was based on the demonstration of a mass in the gallbladder after the administration of a contrast medium. In 3 cases (Cases 1, 3 and 5) in which the gallbladder was not demonstrable at the same time as the mass, the situation of the latter within the gallbladder was concluded from its persistence in the gallbladder region for 2 or more days, from the position of the gallbladder at a later examination, from the characteristic shape of the precipitate at the fundus, and/or from the exclusion of other localizations.

The precipitate could not be distinguished with certainty from limy bile by its roentgenographic appearance alone. It was, however, not seen on examination immediately before or a few days after the administration of contrast medium; in some cases it was observed repeatedly on intake of contrast medium.

A precipitate of contrast medium in the gallbladder may no doubt be easily overlooked. When the gallbladder is not visible, the precipitate may be misinterpreted, e. g. as residues of contrast medium in the bowel. Such residues are known to occur frequently in cholecystography with Telepaque and Bi-Na. Even on satisfactory demonstration of the gallbladder, however, a precipitate may escape recognition. Small amounts lining the lower wall of the gallbladder may be observable only in orthoprojections and the opaque material may be dispersed in the contents of the gallbladder and thereby become temporarily invisible (Cases 2, 4, 7, and 8).

A precipitate of contrast medium has previously been observed in the gallbladder after the administration of iopanoic acid (Telepaque). In the present series, the precipitate was produced by the sodium salt of this substance (Bi-Na) in at least 7 cases. In Case 7 the precipitate was not demonstrated after the ingestion of Bi-Na alone, but only after an additional intake of Pheniodol (Bilitrast). As products of both contrast media were probably then present in the gallbladder, Bi-Na might be responsible for the precipitation in this case as well. The fact that no precipitate was seen on the first day after the administration of the final dose of Bi-Na does not argue against this assumption. (Cf. Case 6.) In spite of its wide-spread use for routine cholecystography Pheniodol is not known to become precipitated in the gallbladder.

Bi-Na is supposed to be converted by the hydrochloric acid in the stomach into iopanoic acid in an amorphous form; this is more easily absorbed than the crystalline form of iopanoic acid in Telepaque (PETERHOFF 1956, and others). After absorption, however, Bi-Na and Telepaque are presumedly identical. In the present series the precipitation was demonstrated in 3 cases after 3 g and in 5 cases after 6 g Bi-Na. When appearing with 3 g of the contrast medium the precipitate did not increase appreciably in amount after the administration of an additional dose.

A precipitation of contrast medium is rarely observed on routine cholecystography. It should be noted, however, that even if carefully sought for, a precipitate will escape recognition if sufficiently small, if dispersed in the bile, or if produced after completion of the examination. Thus, although few cases of the condition are on record, precipitation of contrast medium is not necessarily rare.

Physical properties. No specimen with a precipitate of contrast medium has hitherto been available for physico-chemical analysis. Roentgenographically, the precipitate appeared as a mass which was sometimes irregular in outline and sometimes heterogeneous in opacity. In some patients clear formations within the mass were found to be calculi (Case 3 in the present series and the one previously described), but in others such formations were present although the gallbladder did not contain any concretions before or after the occurrence of a precipitate (Cases 1 and 6). The mass was heavy, and usually situated at the fundus of the gallbladder. In Case 6, however, it persisted for at least several hours as an irregular layer between two fractions of the contents of the gallbladder, fractions of different gravity and miscibility with the dissolved contrast medium. In most cases the precipitate appeared as a cohesive mass with a tendency to adhere to the wall of the gallbladder, though dispersible in the bile. A rather low solubility in bile was apparent from observations

on the persistence of the precipitate. The precipitate was sometimes transiently dispersed and then not demonstrable, but it did not definitely disappear as long as the gallbladder was visible. The gallbladder as a rule was free of the precipitate in a few days; in one patient (Case 6), however, residues of the precipitate were observed more than one month after its production. The possibility of its permanency and even solidification in rare cases cannot be excluded.

Attempts were made in 5 of the cases to reproduce the precipitation of contrast medium by repetition of cholecystography with Bi-Na. In 2 of these the attempts were successful and resulted in essentially similar observations as those made on the first occasion. It seems remarkable that no appreciable difference occurred in the amount, if any, of precipitate formed in a gallbladder on different occasions. In 3 cases attempts to reproduce the phenomenon failed. In one of these (Case 3) this was explained by the inability of the contrast medium to enter the gallbladder. In the others, however, control cholecystography with Bi-Na was normal (Cases 1 and 5).

Relation to gallbladder disease. The patients in the present series had been referred for cholecystography because of clinically suspected gallbladder disease. In all of them cholecystography revealed not only precipitation of contrast medium in the gallbladder but also definitely pathologic changes, i. e. biliary calculi or non-filling of the gallbladder. This also holds true for the case previously reported as having a precipitate in the gallbladder after the administration of Telepaque. Although theoretically possible, it seems less likely that the small amount of precipitate per se should be responsible for any non-filling of the gallbladder by preventing a sufficiently high concentration of contrast medium from being reached in the gallbladder bile. In those cases in which a normal finding was obtained on re-examination (Cases 1 and 5) a definite improvement of the clinical signs and symptoms had occurred in the meantime, which might well explain why the gallbladder was then demonstrable. Judging from the available material, precipitation of contrast medium in the gallbladder after the administration of iopanoic acid or its sodium salt might therefore be indicative of gallbladder disease.

Pseudoconcretions. Despite the definite absence of gallbladder stones, clear formations resembling calculi appeared to be enclosed in the precipitate in 2 cases (Cases 1 and 6). In Case 6 these pseudoconcretions were observed to develop on incomplete and heterogeneous intermixture between the precipitate and some clear fraction of the gallbladder content. They might not have been distinguishable roentgenographically

from true concretions if they had not changed in form and size on subsequent examinations or disappeared entirely.

True concretions were sometimes recognizable by their persistence on disappearance of the precipitate. In Case 3, in which small clear masses were inconstantly demonstrable within the precipitate, their nature could not be determined with certainty before operation. They were regarded as concretions because small calculi had previously been demonstrated in the gallbladder. Operation confirmed the diagnosis.

Production. The precipitate apparently consisted of some part or product of a contrast medium, and in all cases most probably iopanoic acid. Until chemical analysis has been performed, further discussion of the composition and production of the precipitate can only be hypothetical. When excreted by the liver iopanoic acid is said to be linked with glucuronic acid and form a water-soluble compound (McCHESNEY & HOPPE 1954). A high concentration of this compound in the bile is held responsible for the visibility of the gallbladder in cholecystography with Telepaque or Bi-Na. No change in its chemical structure is known to occur in the gallbladder whether this organ be normal or diseased. The precipitate was probably not produced by saturation of a solution of glucuronated iopanoic acid in the present series. The concentration of contrast medium in the bile was never unusually high; in fact in some patients it was not even sufficient to demonstrate the gallbladder roentgenographically. Nor does it seem likely that the glucuronate was precipitated by the absence of any factor governing its solution in the gallbladder bile. Further inflow of the glucuronate would then presumedly have resulted in further precipitation but no increase in the amount of precipitate was demonstrable with increasing dosage of the contrast medium. The low solubility of the precipitate, apparent from the observations on its persistence, seems to provide further evidence that it consisted of some substance other than glucuronated iopanoic acid.

Since gallbladder disease was demonstrable in all cases in which precipitation occurred, some abnormal constituent of the gallbladder bile — or excess of some normal constituent — may have determined the conversion of the contrast medium into a substance of low solubility. If available in a limited amount and reversibly producing the precipitate, such a bile constituent might be able to form the same amount of precipitate on repeated cholecystographic examinations, provided that sufficient contrast medium entered the gallbladder. Without further knowledge of the pathology of bile and the chemical composition of the contrast medium precipitate, however, no clear conception of the factors involved in the precipitation is possible.

SUMMARY

Eight cases are reported in which a precipitate of contrast medium occurred in the gallbladder at cholecystography with the sodium salt of iopanoic acid. In one case it persisted more than one month. The phenomenon was reproducible in 2 out of 5 cases studied. A systematic survey of the roentgenographic findings is included.

ZUSAMMENFASSUNG

Acht Fälle werden berichtet, bei denen ein Niederschlag des Kontrastmittels in der Gallenblase bei der Cholecystographie mit dem Natriumsalz der jopanoischen Säure auftrat. In einem Fall blieb er länger als einen Monat liegen. Das Phänomen konnte in 2 von 5 untersuchten Fällen reproduziert werden. Eine systematische Übersicht über die Röntgenbefunde wird inkludiert.

RÉSUMÉ

L'auteur présente huit cas ou s'est produit un précipité du moyen de contraste dans la vésicule biliaire, après une cholécystographie avec le sel sodique de l'acide iopanoïque. Dans un cas, ce précipité a persisté plus d'un mois. Sur 5 cas étudiés, ce phénomène s'est reproduit dans deux cas. L'auteur fait une revue systématique des signes radiographiques.

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ORAL CHOLEGRAPHY WITH BILIJODON-NATRIUM CAPSULES

An analysis of 96 cases

by

Pekka Virtama

The introduction of intravenous cholegraphy with Biligrafin opened a new era in the roentgenologic examination of the biliary tract although oral cholecystography is still universally used as a routine method in the roentgenologic examination of the biliary tract. The low toxicity and cheapness of the latter method as well as the ease with which it may be carried out, have all contributed to its continued acceptance. Consequently the main indications for the intravenous examination of the biliary tract may now be listed as: defective filling or non-filling of the gallbladder in oral cholecystography, the post-cholecystectomy syndrome (SAMUEL 1955), and pre-operative investigation of the bile ducts.

Some authors, e. g. TWISS et coll. (1954), have reported good outlining of the common bile duct with oral contrast media. These methods have not been used routinely because the frequency and degree of filling of the bile ducts is better with Biligrafin.

The agent mostly used in oral cholecystography is iopanoic acid, γ-etyl-β- (3-amino-2,4,6-tri-iodophenyl)propionic acid (Telepaque, Bilijodon). Bilijodon-Natrium, a sodium salt of iopanoic acid, has recently been

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in roduced by AB Leo, Hälsingborg, Sweden. The advantage of this agent is that being water-soluble it is less likely to remain undissolved in the al mentary tract and is also more readily absorbed from the intestine (F TERHOFF 1956).

GUNNARSON (1958) presented a new method of oral cholegraphy. In 20 cases he introduced 4 g Bilijodon-Natrium dissolved in 20 ml of distilled w ter into the duodenum with the aid of a plastic catheter and after an in erval of 20 to 30 minutes he was able to observe the common bile du t filled with the contrast medium. Later on, 0.45 g of the agent was ad ninistered in the form of gelatin capsules containing a 50 % solution of the contrast medium, and the main bile ducts were demonstrated after 45 min.

The present author's material consists of 96 patients, 23 of them men, who were examined with Bilijodon-Natrium capsules. The oldest patient was 75 and the youngest 19 years of age, the mean age being 46 years. In 60 cases, roentgen examination of the biliary tract had not been previously performed. The gallbladder had not filled in 24 cases following the administration of 6 tablets of Telepaque. Twelve of the patients had undergone cholecystectomy and, in 2 of these, intravenous cholegraphy was carried out 3 to 4 days after the oral examination.

The method of examination was the one given by GUNNARSON (1959): The dose was about 1 g per 20 kg bodyweight, 150 to 500 ml of distilled water being given with the capsules; the patients with a tendency to constipation received more water. After the ingestion of the capsules and distilled water, the patients were placed in the right decubitus position for about one hour. Films were produced after 45, 60, 90, 120, 180, and, in many cases, after 240 min.

Results

It was possible to see that contrast medium had been liberated in the stomach 15 to 20 min after the ingestion of the capsules; thus, the capsules were dissolved rather quickly. The next stage, the passage of the contrast medium from the stomach, was slower, and there were remarkable individual variations. In about 60 per cent of the cases a considerable amount of the contrast medium remained in the stomach after 1 hour, in 20 per cent of cases after 1 $^1/_2$ hours and in some cases even after 3 hours. Contrast remnants were in most cases evident in the stomach after 2 hours.

The time of filling of the bile ducts and gallbladder seemed to be dependent on the emptying rate of the stomach. The filling of the bile ducts started in most cases after 1 hour. The time of maximum filling of the bile ducts occurred in 70 per cent of the cases after 1 $^1/_2$ hours, in 20 per cent after 2 hours, and in the rest of the cases later. In many cases

the bile ducts were still outlined after 3 hours, which was apparently not pathologic.

The filling of the gallbladder commenced in about 60 per cent of the cases simultaneously with the maximum filling of the common bile duct. The gallbladder and the main bile ducts were seen to be well filled in about 40 per cent of the cases after 2 hours. In the successful cases, the filling of the gallbladder was most intense after 3 hours, but in about 15 per cent of the cases after 4 hours. In 5 cases films were taken the next morning, i. e. after 24 hours; in 3 of these cases the gallbladder was still well shown.

The final results of the examinations are recorded in the Table below.

Table

Results obtained in three groups of patients examined after the intake of Bilijodon-Natrium capsules

Findings	In 60 cases not previously examined*		In 24 cases with previous non-filling of gallbladder 12 hours after administration of 6 tablets of Telepaque		In 12 cases with previous cholecystectomy**
	Common bile duct	Gallbladder	Common bile duct	Gallbladder	Common bile duct
No filling	5	2	6	5	1
Poor filling	7	10	8	6	3
Moderate filling.....	24	24	8	10	5
Good filling	24	24	2	3	3

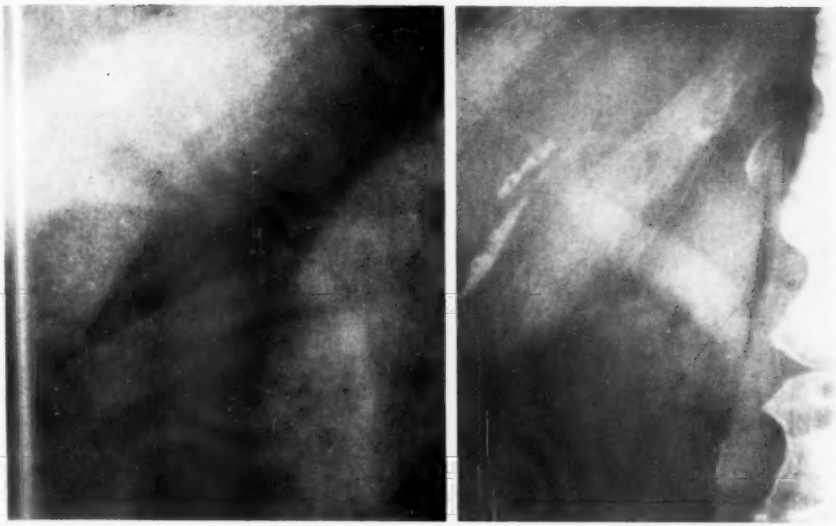
* Gallstones were visible in 3 of the cases.

** Intravenous cholegraphy with Biligrafin was performed in 3 of these cases 3 to 4 days later: in 2 cases the result was slightly better than in the oral examination, in one case no filling was obtained.

Side-effects. The side-effects of iopanoic acid are reported as mild. RENCK (1956) noted vomiting in 3 per cent of cases after the administration of Telepaque. PETERHOFF (1956) observed reactions due to Bilijodon-Natrium tablets; these consisted of vomiting in 4.7 per cent of cases after a dose of 6 tablets, diarrhoea in 7 per cent of cases given 4 tablets and 26 per cent of those receiving 6 tablets. The higher frequency of side-effects with Bilijodon-Natrium was attributed to its rapid absorption and good solubility.

The toxicity of Biligrafin is lower than that of the oral contrast media containing two iodine atoms (FROMMHOLD 1953). However, allergic side-effects such as transient nausea, tachycardia, headache, and even collapse, have been noted (JUNKMANN 1955).

The 96 patients of this material preferred to swallow 4 to 6 large capsules each containing 0.7 g Bilijodon-Natrium rather than almost twice



a b

Fig. 1. a) Poor filling of the common bile duct and its main branches at 1 hour after the intake of 5 capsules of Bilijodon-Natrium. b) Moderate filling of the common bile duct at 2 hours in a patient who had undergone cholecystectomy.

the number of smaller capsules containing 0.45 g of the drug. Seventy-two cases were examined with 1 g/20 kg bodyweight Bilijodon-Natrium. In 40 of these, no side-effects were observed; of the remaining 32 cases, a burning sensation occurred in 8, nausea in 8, vomiting in 7, diarrhoea in 7, and dizziness in 2 cases. Twenty-four cases were examined with 6 tablets of Telepaque, followed 12 hours later by 3 capsules of 0.7 g Bilijodon-Natrium. In 11 of these, no side-effects were noted; of the remaining 13 cases, a burning sensation occurred in 1 case, nausea in 4 cases, vomiting in 2, diarrhoea in 2, dizziness in 3, and collapse in 1 case.

The reactions after 6 tablets of Telepaque and an additional dose of 3 capsules of Bilijodon-Natrium were apparently not due to the contrast media alone. Among other things, the long fast of 12 to 16 hours and the evacuation of the bowels made these patients more disposed to reactions.

Nine patients received ice-cold distilled water of 2 g sodium bicarbonate after the ingestion of the capsules. The effect of these measures was disappointing. A spasmolytic agent (Buscopan) was given intravenously in some cases with good effect.

Fig. 2. Good filling of the gallbladder and the common bile duct at 3 hours after the intake of Bilijodon-Natrium capsules.

Discussion

The demonstration of the biliary tract was definitely more rapid and more complete with Bilijodon-Natrium capsules than with the conventional oral media. The most important advantage was the outlining of the main bile ducts, the results being comparable with those achieved in intravenous cholegraphy with Biligrafin. However, in the latter case, the main bile ducts are filled with the contrast medium about 1 hour sooner, the maximum filling of the gallbladder taking place in both methods after about 3 to 4 hours from the beginning of the examination (see HORNYKIEWYTSCH and STENDER 1954). The main advantage of Bilijodon-Natrium over Biligrafin was the homogeneous filling of the gallbladder without any disturbing sedimentation.

As a routine method for roentgen examination of the biliary tract, oral cholegraphy has the same disadvantages as intravenous cholegraphy in being more complicated and time-consuming than conventional oral cholecystography; furthermore, the risk of side-effects is increased. When the ordinary oral cholegraphic agent failed to fill the gallbladder, an additional dose of 3 capsules of Bilijodon-Natrium was given which in most of these cases rendered it possible to make a final diagnosis without repeat examinations.

The side-effects noted in about 50 per cent of the cases examined were of a mild and transient nature. The frequency of the reactions recorded is perhaps rather too high by reason of the fact that even the mildest symptoms were registered.

Although the final value of the new method remains to be assessed, new possibilities for roentgen departments to deal with their everyday problems can be foreseen. At about the same cost, the method gives more information about the biliary tract than ordinary oral cholecystography, its disadvantages, however, being an increased risk of side-effects and a prolonged examination time.

SUMMARY

Oral cholegraphy with Bilijodon-Natrium capsules was found to be comparable with intravenous cholegraphy with Biligrafin in a material of 96 cases. The side-effects were rather frequent although mild and transient. Oral cholegraphy proved to be valuable as an additional method in those cases in which the ordinary oral contrast media had failed to produce filling of the gallbladder.

ZUSAMMENFASSUNG

Die orale Cholegraphie mit Bilijodon-Natriumkapseln wurde in einem Material von 96 Fällen als mit der intravenösen Cholegraphie mit Biligrafin vergleichbar gefunden. Nebenwirkungen kamen ziemlich oft vor; sie waren jedoch milde und flüchtige. Die orale Cholegraphie erwies sich als zusätzliche Methode in den Fällen als wertwoll, in welchen die üblichen oralen Kontrastmittel keine Füllung der Gallenblase erzeugen konnten.

RÉSUMÉ

Sur une série de 96 cas, la cholégraphie par voie orale au moyen de capsules de sel de Bilijodon-Natrium a donné des résultats comparables à ceux de la cholégraphie intraveineuse par la Biligrafin. Les effets secondaires ont été assez fréquents, mais bénins et passagers. Cette cholégraphie orale s'est montrée utile comme méthode complémentaire dans les cas où le moyen de contraste oral ordinaire n'a pas opacifié la vésicule biliaire.

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EFFECT OF ROENTGEN IRRADIATION OF LYMPHOCYTES IN VIVO

by

G. H. Hjort

It was shown in 1904 (HEINKE) that lymphatic tissue exhibited a marked response to roentgen irradiation; the lymph follicles disappeared and the cells presented signs of damage. The changes in the lymphocytes have been investigated more recently by several methods. SCHRECK (1947) demonstrated by dark-field microscopy that lymphocytes exposed to roentgen rays showed an increase of granules and vacuoles in the cytoplasm. SCHRECK later (1955) observed suspensions of thymus by phase contrast microscopy and a cinematographic technique, the cells being irradiated in vitro with a dose of 10 000 r and incubated at 37° C. The first signs of degenerative changes appeared 1 hour after irradiation as slight irregularities in the shape of the nucleus, and occasionally cytoplasmic changes such as the formation of small vacuoles or thin cytoplasmic filaments; ten minutes later the rhythmic movements of the cells suddenly ceased. Irradiation with 1 000 r (SCHRECK 1957) under similar conditions produced rather different changes which commenced 2 hours after irradiation, i. e. the formation of single or multiple intranuclear vacuoles followed by slight irregularity in the shape of the nucleus, which later became pycnotic. SCHERER and WICHMANN investigated lymphocytes and reticulum cells by phase contrast microscopy after roentgen irradiation and one hour

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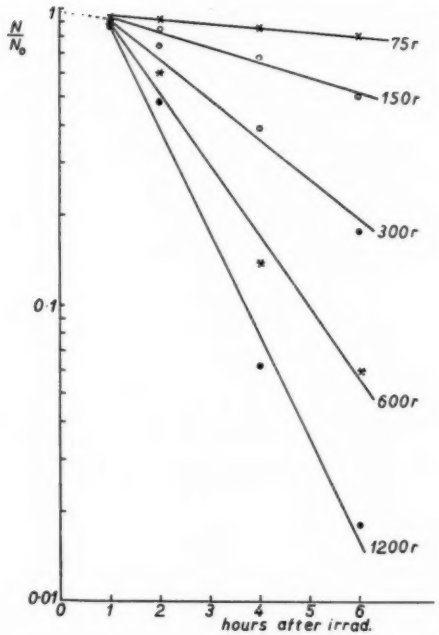

Diagram 1. Time-effect curves for varying roentgen doses. Ordinate: Fraction of surviving cells. Abcissa: Time in hours.

after irradiation with 200 to 800 r found changes in both the nuclei and mitochondria. The nuclei showed clumping of chromatin and, after from 12 to 48 hours, formation of intranuclear vacuoles; the nuclear membrane was often thicker than normal and the nucleoli were generally enlarged and irregularly shaped; the mitochondria were distended one hour after irradiation and disappeared in degenerated cells. HUMBLE, JAYNE, PULVERTAFT and WILSON cultivated lymphocytes from tumorous lymph gland after irradiation with doses varying from 30 to 712 r. The first changes were noted after 6 hours as darkening of the nucleus by phase contrast; in the dark area a cyst developed and cytoplasmic details disappeared. These investigations indicate that the first morphologic changes in the lymphocytes appear about 1 hour after irradiation, but it does not seem clear whether they appear first in the nuclei or in the mitochondria.

ACKERMAN has shown that histochemical changes such as a decrease in the alkaline phosphatase and the sulphydryl groups, particularly the former, occur prior to the morphologic changes. PATT et coll. found that

Table 1

Mean survival time of lymphocytes and number of undamaged cells at different times after irradiation

Irradiation dose	$\frac{T}{2}$ hours	τ hours	Time after irradiation	Number of undamaged cells per 1000				
				75 r	150 r	300 r	600 r	1 200 r
75 r	17.15	24.85	1 hour	959	959	937	905	897
150 r	5.45	7.89	2 »	928	858	759	609	483
300 r	2.45	3.26	4 »	866	684	399	135	63
600 r	1.30	1.89	6 »	818	513	175	58	18
1 200 r	0.90	1.31						

an increase in the percentage of eosin-stainable thymocytes occurred following irradiation; the surviving cells were eosin-resistent.

TROWELL has used the number of lymphocytes with pycnotic nuclei as a quantitative measurement of irradiation damage. A method similar to TROWELL's in vitro method has been used in the present work.

Method and Material

Wistar rats weighing 150 g were employed for the experiments. The rats were placed in a box and irradiated with a dose varying from 75 to 1 200 r. As shown by DOUGHERTY and FRANK stress stimuli can cause various changes in the lymphocytes and control animals were therefore carried through the whole irradiation procedure without being irradiated. They were then killed 1 to 6 hours after the sham irradiation.

The rats were killed by skull fracture at intervals varying between 1 and 6 hours after irradiation. A lymph node from the neck was removed and placed on a microscope slide in a drop of 0.9 % NaCl. The tissue was then minced with a knife and a drop of the fluid transferred to a clean microscope slide upon which it was spread in a thin layer; it was then immediately fixed in Susa fluid and, after fixing, stained in Harris hematoxylin. A thousand cells were counted in each preparation and the number of cells with pycnotic nuclei or intranuclear vacuoles registered as damaged cells.

Results

Time-effect curve. Plotting of the time-effect curve for different roentgen doses (Diagram 1) shows that the surviving fraction of the cells decreases exponentially after a latent period of about 1 hour. One may

Table 2

Cell counts at different times after irradiation

Dose	Time after irradiation							
	1 hour		2 hours		4 hours		6 hours	
	% damaged cells	Probit	% damaged cells	Probit	% damaged cells	Probit	% damaged cells	Probi
75 r	4.1	3.26	7.2	3.54	13.4	3.89	18.2	4.09
150 r	4.1	3.26	14.2	3.93	31.6	4.52	48.7	4.97
300 r	6.3	3.47	24.1	4.30	60.1	5.26	82.5	5.93
600 r	9.5	3.68	39.1	4.72	86.5	6.10	94.2	6.57
1 200 r	10.3	3.73	51.7	5.04	93.7	6.53	98.2	7.10

assume that chemical events take place inside the cells during the latent period, and that these commence to be morphologically visible after 1 hour. By using the commencement of the disintegration period as the morphologic zero point we obtain a curve from the formula:

$$N = N_0 \cdot e^{-\alpha t}$$

From this we can find the mean survival time of the lymphocytes after irradiation

$$\tau = 1.45 \frac{T}{2}$$

where $\frac{T}{2}$ is the half value time and can be read from the curve.

It will be seen from Table 1 that the mean survival time of the lymphocytes decreases rapidly with increasing dose.

The cells used for the pycnotic count are small lymphocytes or cells which are morphologically indistinguishable from this cell type. The fact that the curve after the latent period is of a simple exponential form indicates that the cells are physiologically of one cell type or of two or more types with the same radio-sensitivity, of which the first possibility seems to be more likely. If the cells formed a heterogenous group with different sensitivities the curve should be of the multiple exponential form.

Dose-effect curve. The dose-effect curve for lymphocytes has been shown by TROWELL to form a straight line when plotted on logarithmic probability paper.

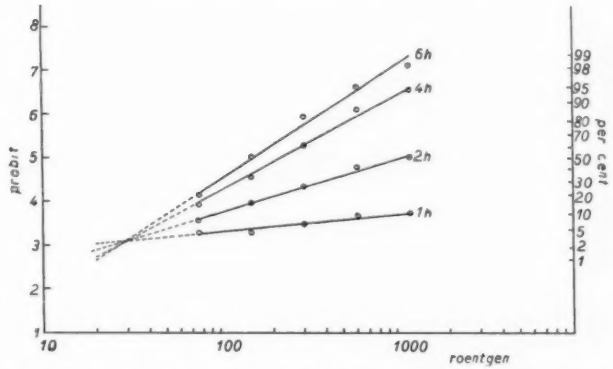

Diagram 2. Dose-effect curves at different times after irradiation. Ordinate: % damaged cells (right), probit (left). Abscissa: Dose in roentgen.

Diagram 2 shows the effect curve, with logarithmic dose as abscissa and frequency of pycnotic cells as ordinate, the different curves representing different times in hours after irradiation. The LD_{50} doses are given in Table 2. It will be seen from the diagram that the curves cross each other at a point corresponding to a dose of 30 r. This would seem to indicate that 30 r is the lowest dose which produces a significant increase in the number of cells with pycnotic nuclei. This is in good agreement with the findings of HUMBLE et coll., who found that the threshold dose required to produce visible changes in lymphocytes in vitro was 30 r.

In the present experiment it was not possible to follow the changes in the lymphocytes longer than 6 hours, as after that time large, often multinucleated, phagocytes appeared in the lymph nodes and removed the damaged cells.

SUMMARY

The numbers of pycnotic lymphocytes were counted in smears from the cervical lymph glands of rats following roentgen irradiation. The time-effect curve showed a latent period of 1 hour, and thereafter the fraction of normal cells fell exponentially with time. The percentage dose-effect curve followed a straight line on logarithmic probability paper; from this the LD_{50} dose could be calculated.

ZUSAMMENFASSUNG

Nach Röntgenbestrahlungen von Ratten wurde die Anzahl pyknotischer Lymphozyten in Ausstrichen von Halslymphdrüsen gezählt. Die Zeit-Effektkurve zeigte eine Latenzzeit von einer Stunde; danach fiel die Fraktion normalen Zellen exponentiell mit der Zeit ab. Die prozentuelle Dosis-Effektkurve gab auf Logarithmenpapier eine gerade Linie von der die LD 50-Dosis berechnet werden konnte.

RÉSUMÉ

L'auteur a compté, après irradiation roentgen, le nombre de lymphocytes pycnotiques sur des frottis de ganglions lymphatiques cervicaux du rat. La courbe effet-temps montre une période de latence d'une heure, après laquelle la proportion de cellules normales diminue exponentiellement en fonction du temps. La courbe effet-dose est une ligne droite, sur papier logarithmique, permettant de calculer la DL_{50}.

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MODIFICATION DE L'ERYTHROPOIESE APRES RADIOTHERAPIE PELVIENNE

par

M. Tubiana, C. I. Bernard et *C. Lalanne*

Divers processus peuvent être évoqués pour expliquer le mécanisme de l'anémie qui apparaît fréquemment chez les sujets irradiés; celui qui paraît le plus directement en cause est une dépression fonctionnelle de la partie du système érythropoïétique qui se trouve dans le volume irradié. Les troubles hématologiques qui se manifestent de façon particulièrement fréquente après l'irradiation à dose élevée des tumeurs pelviennes sont souvent rapportés à une action directe des radiations sur le sacrum, os volumineux et éminemment érythropoïétique. Cette hypothèse nous a paru mériter discussion et vérification.

Pour tester l'activité fonctionelle du tissu érythropoïétique, nous nous sommes adressés au métabolisme du fer qu'il est relativement facile d'étudier par le Fe^{59}. Rappelons schématiquement que le fer plasmatique est transporté par une beta-globuline, la sidérophyline; il est fixé par la moelle qui l'utilise à la synthèse de l'hémoglobine; sous cette forme il sort de la moelle, incorporé dans l'hémoglobine des hématies qu'il ne quitte que lors de leur destruction, environ 120 jours plus tard.

Nous nous sommes proposés d'étudier les modifications apportées par l'irradiation sur le métabolisme du fer par l'ensemble de l'organisme, et sur le métabolisme local du fer dans la région médullaire irradiée et dans les territoires non irradiés.

Soumis à la Rédaction le 2 février 1959.

Matériel et méthodes

Cette étude a été faite sur 9 sujets qui ne présentaient pas d'hémorragie macroscopique et chez qui toute thérapeutique martiale avait été proscrite. Il s'agissait dans 7 cas d'un épithélioma du col au stade III; 2 autres patientes avaient subi auparavant une exérèse, l'une pour tumeur bilatérale des ovaires, l'autre pour tumeur intestinale. L'exploration au radio-fer a été faite une semaine avant l'irradiation, puis répétée environ 2 mois plus tard, à la fin de l'irradiation. Une malade a reçu la seconde injection de Fe^{59} 2 mois et demi après la fin du traitement. Un troisième test au fer a été effectué chez une seule malade, 1 an après l'irradiation.

Les malades ont été traitées en télécobalt-thérapie par cyclothérapie complète ou pendulaire, ou par champs fixes et ont reçu une dose de 6 000 r dans le volume-cible qui contient toute la cavité pelvienne. Le sacrum est, au moins partiellement, en dehors de ce volume, mais à son voisinage immédiat; la dose y est quelque peu variable de 4 000 à 6 000 r.

L'utilisation des rayons gamma du cobalt 60 (énergie moyenne 1,25 MeV) présente plusieurs avantages: il est possible d'atteindre des doses tumorales élevées sans incident cutané et avec une dose intégrale plus faible qu'en radiothérapie classique; le volume irradié est géométriquement bien délimité; la dose absorbée (en rads) par le tissu osseux et le tissu médullaire est en relation mieux définie avec la dose d'exposition (en 'roentgens') que pour les rayonnements de plus faible énergie (pour les gamma du cobalt 60, 1 r correspond sensiblement à une dose absorbée de 1 rad).

Les techniques utilisées sont identiques à celles précédemment décrites (Schapira 1954, Boiron 1955 et Meeus-Bith 1957).

Le radio-fer utilisé Fe^{59} (période T = 45 jours), est livré par Oak-Ridge avec une activité spécifique de 2 microcuries par microgramme de fer; il est utilisé sous forme de perchlorure en solution milli-normale, non tamponnée. Il est lié à 10 ml de plasma du sujet, au cours d'une incubation à 37°, pendant 45 minutes. Des électrophorèses ont montré que le radio-fer est alors fixé sur les beta-globulines. Le plasma marqué est injecté par voie intraveineuse; l'activité utilisée est de l'ordre de 15 microcuries par malade.

Mesures

L'exploration comporte 2 séries de mesures qui s'adressent au métabolisme du Fe^{59} pour l'ensemble de l'organisme et au métabolisme local pour différents territoires.

A. Mesure de la radioactivité du sang

Les ponctions sanguines débutent à la 5ème minute, temps au bout duquel on peut admettre une homogénéisation de la concentration plasmatique. Elles sont répétées à intervalles réguliers pendant 2 h. 30, puis à la 24ème heure, et tous les 2 jours pendant au moins une semaine. Un hématocrite et un dosage de fer sérique sont effectués au moment de l'injection. La radioactivité du sang et du plasma est mesurée au compteur à scintillation à cristal creux et est rapportée à un echantillon de 1 ml.

On détermine, sur la courbe représentant la variation de la concentration du Fe^{59} plasmatique et qui montre une décroissance exponentielle en fonction du temps, les facteurs suivants:

1. *La période de disparition du* Fe^{59} plasmatique qui est le temps au bout duquel la concentration est réduite à moitié.

2. *Le taux de renouvellement du fer plasmatique.* Il représente la quantité de fer qui, en un jour, quitte le plasma pour passer dans la moelle ou dans les réserves. Pour éviter la détermination du volume plasmatique, le taux de renouvellement est rapporté à 100 ml de sang.

Si C est la concentration du fer plasmatique stable (en μg/100 ml) la quantité de fer (mesurée en μg) qui sort du plasma (100 ml) par minute est $C \times \frac{0,693}{T_{min}}$, soit par jour $C \times \frac{0,693}{T_{min}} \times 60 \times 24$ ce qui est sensiblement égal à $1\,000 \frac{C}{T_{min}}$.

Le taux de renouvellement relatif à 100 ml de plasma peut être rapporté à 100 ml de sang en le multipliant par (1 — H) où H est l'hématocrite veineux (corrigé).

En définitive, le taux de renouvellement R du fer en mg pour 100 ml de sang et par jour est

$$R = \frac{\text{concentration du fer plasmatique en } \mu g/100 \text{ ml de plasma}}{\text{période de disparition en minutes}} \times (1 - H).$$

(La valeur moyenne de ce taux de renouvellement chez les sujets normaux est 0,61 (BOTHWELL).)

3. *L'incorporation du fer 59 dans les hématies.* Après la rapide disparition initiale du fer 59 plasmatique on assiste dans les jours qui suivent l'injection à sa réapparition dans le sang où il est véhiculé par les G.R. marqués. La variation de l'activité sanguine permet d'apprécier la vitesse de l'incorporation du Fe^{59} dans les hématies ainsi qui le taux de cette incorporation. Ce dernier est défini par le rapport de l'activité de 1 ml de sang à l'activité à l'instant de l'injection; celle-ci est évaluée par extra-

polation à zero de la courbe de décroissance de l'activité sanguine. (Chez les sujets normaux le taux d'incorporation passe par un maximum entre le 7ème et le 10ème jour où il atteint une valeur de l'ordre de 80 %.)

B. Measures externes du Fe^{59} dans différents territoires

Les mesures externes de la radioactivité sont faites par comptage en regard de quelques régions, à l'aide d'un compteur à scintillation à cristal d'iodure de sodium de 5 cm d'épaisseur, protégé par un collimateur de plomb de 7 cm d'épaisseur (MEEUS-BITH 1957).

Elles débutent dès la 4ème minute après l'injection et sont alors effectuées aussi rapidement que possible.

Les points mesurés sont: la base du sacrum, la première pièce sternale, la 4ème côte droite, ou la première vertèbre dorsale, la rate dans le 9ème espace intercostal sur la ligne axillaire antérieure, le foie dans le 9ème espace intercostal sur la ligne mamelonnaire.

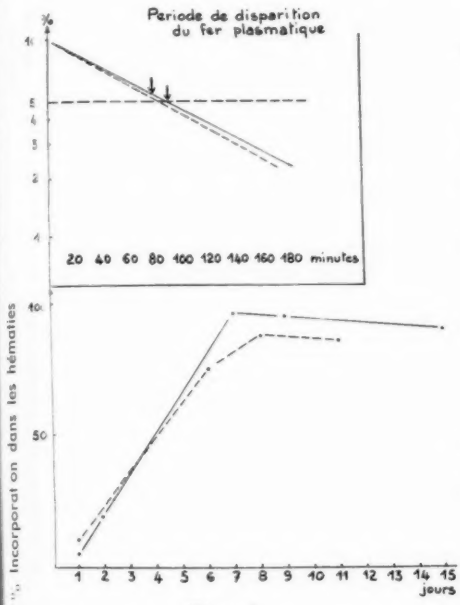
Les mesures sont répétées 2 h. 30 après l'injection, puis les mêmes jours que pour les prises de sang.

Pour chaque point les conditions géométriques sont bien définies et aisément reproductibles.

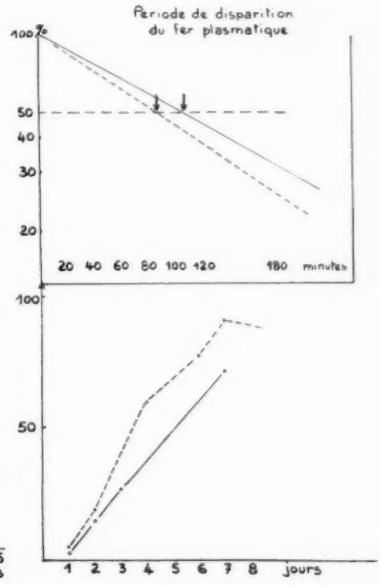
Pour étudier la variation de la radioactivité dans le tissu médullaire il est nécessaire d'effectuer une correction pour soustraire du comptage la partie qui est dûe à la radioactivité du sang contenu dans le volume qui est »vu» par le compteur.

On admet qu'à la première mesure (4ème minute) la fixation sur la moelle est encore nulle et que le taux de comptage est alors uniquement dû à la radioactivité du sang circulant. Les conditions géométriques étant fixes et les conditions anatomiques ne pouvant pas présenter de grandes variations, on admet pour les mesures ultérieures que le nombre de coups/minute dû au sang, évolue à partir de cette valeur initiale de façon proportionnelle à la radioactivité sanguine mesurée sur les échantillons. Le nombre de coups/minute ainsi calculé à l'instant d'une mesure est déduit du nombre de coups/minute brut obtenu à cet instant. — Cette méthode que nous avons utilisée précédemment (MEEUS-BITH 1957) est analogue à celle préconisée par HUFF et coll. (1951). —

Cette correction a été déterminée par une mesure à la 4ème minute en regard du sacrum. Il eut été souhaitable que la mesure initiale ait été aussi précoce pour chacun des territoires étudiés mais ceci nécessiterait pratiquement un appareil de comptage pour chacun de ces points et n'a pû être réalisé. Les diverses mesures initiales en regard des différents territoires explorés se sont en fait échelonnées sur 20 minutes. La correction est d'autant moins rigoureuse que la mesure initiale est plus


Période de disparition du fer plasmatique
%
20 40 60 80 100 120 140 160 180 minutes
% Incorporation dans les hématies
50
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
jours

Diagr. 1



Diagr. 2

Diagramme 1. Disparition du fer plasmatique (en coordonnée semi-logarithmique) et incorporation du fer radioactif dans les hématies. Chez cette malade (Cas 2), la période de disparition du fer plasmatique, la vitesse et le taux maximum d'incorporation du fer dans les hématies ne présentent pas de modifications importantes après irradiation.

Diagramme 2. Chez cette malade (Cas 6), on constate après l'irradiation un raccourcissement de la période de disparition du fer plasmatique, une accélération de l'incorporation dans les hématies et une élévation du taux de cette incorporation (au 6ème jour).

—— Avant traitement. - - - - Après traitement.

tardive. Cependant, la durée totale de ces mesures est généralement assez brève devant la période de disparition du fer plasmatique pour que l'on puisse admettre que la fixation médullaire est relativement limitée. D'ailleurs l'ordre des mesures est le même au cours des 2 explorations qui ont été effectuées et comme il s'agit essentiellement d'une comparaison de ces 2 tests le risque d'erreur est de ce fait assez faible.

Les mesures sont exprimées arbitrairement en c/minute; les valeurs relatives pour 2 territoires différents sont sans signification car les conditions géométriques du comptage sont différentes. Pour un même territoire ces conditions sont reproductibles et les comptages sont proportionnels à la concentration du Fe^{59} dans le tissu médullaire; pour permettre une comparaison valable pour le même territoire lors de 2 tests

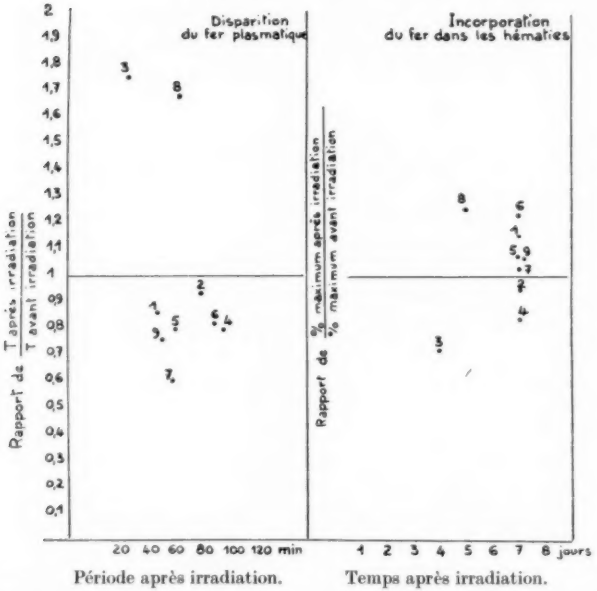


Diagramme 3. Résultats globaux. Dans la partie gauche de la figure, la position de chaque point (correspondant à 1 malade) représente: en abscisse la période après irradiation, en ordonnée le rapport des périodes après et avant irradiation. En règle générale la période est raccourcie après irradiation. Dans la partie droite de la figure, la position d'un point représente: en ordonnée le rapport des taux d'incorporation après et avant irradiation, en abscisse le temps auquel ce rapport a été établi. En règle générale le taux d'incorporation est augmenté après irradiation.

successifs les comptages sont rapportés à une même activité injectée (correspondant à 10^6 c/min comptés dans des conditions géométriques définies). Pour mieux comparer les activités relatives des tissus érythropoïétiques du sacrum et du sternum nous avons calculé au cours de chaque exploration le rapport activité sacrum/activité sternum. Ce rapport n'a de signification que pour un malade et dans des conditions de mesures précises. Sa comparaison au cours de 2 explorations successives chez un même malade permet d'évaluer la variation relative de l'activité de ces 2 territoires.

Répétition du test. Un test au Fe^{59} est effectué pour chaque malade au début de la radiothérapie, puis à la fin. Lors du 2ème test il est nécessaire de tenir compte de la radioactivité résiduelle du 1er test; celle-ci se trouve fixée sur les hématies et se modifie peu pendant la durée du 2ème test. Il suffit d'effectuer avant la 2ème injection une série de mesures pour déterminer la correction à appliquer aux mesures ultérieures.

Resultats

A. Mesures de la radioactivité du sang

1. *Période de disparition du Fe^{59} plasmatique.* Avant l'irradiation, les valeurs de la période s'inscrivent dans les limites normales, c'est-à-dire entre 60 minutes et 110 minutes, chez 7 sujets. Chez 2 sujets, cette valeur est inférieure à la normale: 20 minutes dans le Cas 3 et 38 minutes dans le Cas 8.

Après irradiation dans le Cas 2, les résultats sont pratiquement inchangés (Diagramme 1). Chez 6 sujets, la période de disparition du fer est raccourcie (Diagramme 2); elle est allongée dans les Cas 3 et 8. Ainsi on constate le plus habituellement, un raccourcissement de la période (Diagramme 3).

2. *Taux de renouvellement du fer plasmatique.* Il n'a été calculé que chez 4 sujets chez qui le fer sérique avait été dosé avant et après traitement. Le taux de renouvellement est légèrement augmenté après irradiation, chez 3 sujets. Il est ralenti dans un seul cas où l'exploration a été effectuée 2 mois et demi après irradiation. Un an après irradiation dans le Cas 7, on note le retour au chiffre antérieur à l'irradiation (Tableau).

3. *Incorporation du Fe^{59} dans les hématies.* On a, chez 7 sujets, comparé le pourcentage d'incorporation du radiofer dans les hématies du 7ème jour. Ces comparaisons ont dû être faites le 5ème jour pour le Cas 8 et le 4ème jour pour le Cas 3.

Chez 3 sujets, l'incorporation du fer est nettement augmentée par rapport à la première exploration (Cas 1, 6, 8), une légère augmentation est notée dans les Cas 5 et 9 et on peut constater qu'il n'y a pratiquement pas de changement pour les Cas 7 et 2. Par contre, dans les Cas 3 et 4 on observe une diminution de l'incorporation du fer dans les hématies.

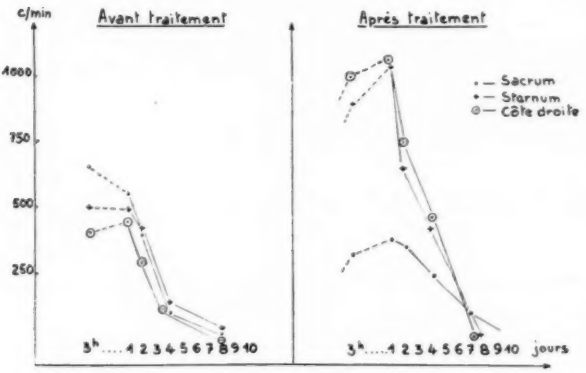
Cette diminution est dans le Cas 3 en concordance avec l'allongement de la période de disparition du fer et traduit donc une baisse de l'activité hématopoïétique.

Ces résultats sont rapportés dans le Tableau; sur le Diagramme 3 sont indiqués les rapports des taux d'incorporation avant et après irradiation.

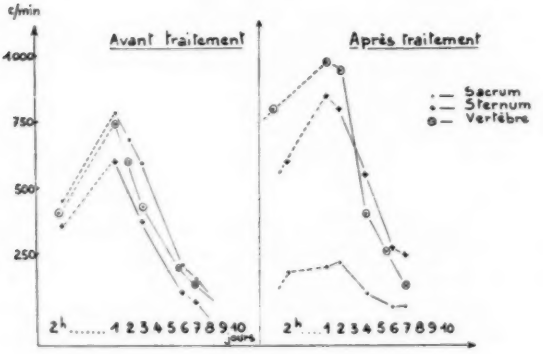
B. Mesures externes de radioactivité

Les courbes de fixation du radio-fer dans les tissus hépatospléniques nous permettent d'évaluer leur mode de participation à l'érythropoïèse. Les courbes du foie et de la rate ne sont pas, dans leur ensemble, modifiées après irradiation.

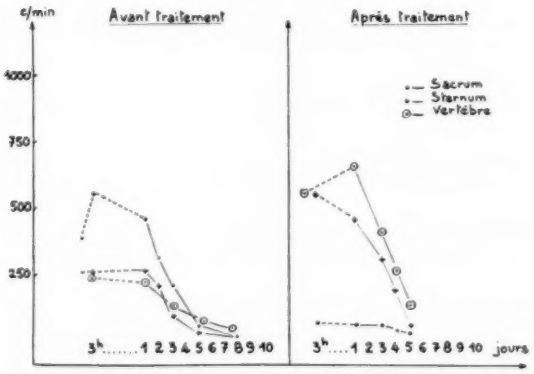
Diagr. 4



Diagr. 5



Diagr. 6



Diagrammes 4, 5, et 6. Mesures externes (Cas 6, 7, 8). Les comptages effectués en regard de divers territoires médullaires montrent après irradiation une diminution de la radioactivité du sacrum et une augmentation de celle des autres territoires.

Au niveau des os explorés on observe de façon constante deux ordres de faits: d'une part, une hypo-activité accentuée au niveau du sacrum irradié qui se traduit par un abaissement du sommet de la courbe et une pente de décroissance plus allongée, d'autre part, au niveau des autres régions médullaires, une activité accrue par rapport à celle de la première exploration (Diagramme 4 et 5).

Le rapport des activités maxima du sacrum et du sternum est donné dans le Tableau. On remarque que ce rapport est nettement plus bas après irradiation; il est près de 10 fois inférieur dans 3 cas.

L'hypoplasie du sacrum a été constatée dans tous les cas et on peut même parler d'aplasie dans le Cas 8.

Nous avons donné les résultats obtenus chez deux sujets, 2 mois et demi après irradiation (Cas 9) et un an après irradiation (Cas 7). Chez ce dernier, le test comparé à celui effectué en fin de traitement, montre une légère remontée du rapport sacrum-sternum.

C. Les numérations globulaires

Les résultats des numérations au début et à la fin du traitement sont donnés dans le Tableau.

Les globules rouges. Dans l'ensemble, le taux des hématies paraît stable pendant la période d'irradiation; dans 2 cas, il existe une chute passagère au début mais le nombre des globules rouges remonte et atteint le chiffre initial. Chez le sujet 7, on a pu noter une baisse globulaire modérée seulement en fin d'irradiation. Dans le Cas 1 une importante chute globulaire se manifeste dès le début et paraît se maintenir jusqu'à la fin de l'irradiation.

Les globules blancs. On a noté dans 5 cas une chute des leucocytes entre le début et la fin de l'irradiation. Il est possible que cette chute soit dûe à la diminution du processus infectieux local mais elle est plus vraisemblablement en rapport avec l'irradiation comme l'a montré une étude systématique effectuée sur un beaucoup plus grand nombre de cas (Abbatucci 1958).

Un seul cas de leucopénie persistante a été constaté chez le sujet 6, chez lequel le chiffre des globules blancs tombe de 3 700 à 1 600 dès le début de l'irradiation.

Les plaquettes. Une diminution des plaquettes est constatée chez 4 sujets, dès le début ou la fin du traitement, mais il ne semble pas que cette diminution soit significative.

Discussion

Les résultats de cette étude montrent de profondes modifications du métabolisme du fer après irradiation partielle de l'organisme.

Tableau

Resultats généraux

Sujets	Hématologie							
	Hématies		Leucocytes		Plaquettes		[6]Hématocrite	
	a	b	a	b	a	b	a	b
1	4350 000	3170 000	11 000	8 000	—	—	34,6	39
2	3700 000	4000 000	5 600	5 200	—	—	36,4	36
3	3800 000	3800 000	13 400	4 800	—	—	30	30
4	4080 000	4030 000	4 600	4 400	—	—	39	30
5	4450 000	3770 000	5 500	3 000	120 000	60 000	36,4	35,5
6	3530 000	3540 000	3 400	1 700	320 000	220 000	41	36,4
7	4500 000	3500 000	9 500	3 500	175 000	110 000	38	39
7d	—	4100 000		4 400	—	196 000	—	38
8	4200 000	4600 000	5 600	7 000	204 000	144 000	34,6	34,6
9c	4030 000	4600 000	3 000	4 400	140 000	270 000	41	39,5

a — avant irradiation
b — à la fin de l'irradiation
c — 2 mois $\frac{1}{2}$ après irradiation
d — 1 an après irradiation

[1] Période de disparition du fer plasmatique
[2] Fer sérique microgrammes p. 100cc. de plasma
[3] Taux de renouvellement du fer/mg/jour/100cc de sang

Le fait le plus net est la baisse importante de l'activité fonctionnelle des territoires érythropoïétiques dans les territoires irradiés; cette défaillance fonctionnelle qui n'avait jamais été notée chez l'homme parait être constante et confirme les résultats des études histologiques et cytologiques qui avaient montré une aplasie de la moelle osseuse dans les territoires irradiés (DENSTAD 1943, STEWART 1956).

On a observé chez l'animal (BELCHER, MAISIN) une diminution de l'activité érythropoïétique des territoires irradiés après irradiation partielle de l'organisme, mais les conditions expérimentales sont alors généralement très différentes car seule une petite partie de l'organisme est protégée contre les radiations alors que chez l'homme, seule une petite fraction de l'organisme est irradiée. Cette différence des conditions d'irradiation explique peut-être pourquoi alors que chez l'animal la récupération fonctionnelle des territoires irradiés est rapide, il semble que chez l'homme dans les 2 cas où nous avons pu effectuer des mesures tardives (2 mois et un an après la fin de l'irradiation) cette récupération ne soit que très faible si elle existe.

Il existe une augmentation importante de l'activité fonctionnelle dans les territoires non irradiés qui est mise en évidence par une augmenta-

Métabolisme du fer									
[1]T. minutes		[2]Fer sérique		[3]R/mg/j/100		[4]I %		[5]Rapport $\frac{\text{sacrum}}{\text{sternum}}$	
a	b	a	b	a	b	a	b	a	b
55	47	—	—	—	—	76	87	1,6	0,20
85	80	—	—	—	—	90	85	1,2	0,5
20	35	—	—	—	—	82	60	1,05	0,20
120	95	—	—	—	—	95	80	1,5	0,57
75	60	—	—	—	—	83	89	1,5	0,25
110	90	158	142	0,85	1	73	90	1,35	0,30
95	58	120	120	0,78	1,25	80	82	1,3	0,33
—	36	—	46		0,79		86		0,45
38	64	38	98	0,65	1	70	88	2,1	0,10
66	50	110	68	0,97	0,79	83	88	1,55	0,20

[4] % d'incorporation du fer dans les hématies

[5] Rapport $\frac{\text{sacrum}}{\text{sternum}}$ à 24ème heure

[6] Ht X 0,91

tion de la quantité de fer radioactif fixé dans les os dans ces territoires. Un phénomène de ce type a également été noté chez l'animal, il correspond vraisemblablement à une hyperactivité compensatrice des tissus non irradiés.

En raison sans doute de cette activité compensatrice le renouvellement du fer plasmatique et l'incorporation du radiofer dans les hématies, ne révèlent généralement aucune diminution de l'activité érythropoïétique globale. Dans 7 cas sur 9, il y a au contraire accélération de la vitesse de disparition du fer plasmatique, et dans 5 cas le pourcentage d'incorporation du fer dans les globules rouges est égal ou augmenté. Au total, dans 1 cas seulement (Cas 3) il semble exister une diminution de l'activité érythropoïétique contrairement à ce qui s'observe chez les malades après radiothérapie globale de l'organisme où l'érythropoïèse semble nettement diminuée (SINCLAIR 1958, LOEFFLER 1957, SUIT 1957). Chez des sujets irradiés de façon partielle, LOEFFLER (1957) n'avait également pu trouver de modification nette des renouvellements plasmatiques. Ces faits suggèrent l'existence d'un mécanisme régulateur qui pourrait fréquemment même dépasser son but et laisser s'établir une sorte de surcompensation.

C'est sans doute en raison de ces faits que nous n'avons pas observé d'anémie chez les sujets irradiés, résultat qui confirme l'analyse des réactions hématologiques effectuée sur un beaucoup plus grand nombre de sujets irradiés (ABBATUCCI 1958) qui avait montré que le nombre de globules rouges ne variait pas de façon statistiquement significative au cours d'une radiothérapie alors que le nombre de leucocytes diminuait régulièrement.

Cependant, il ne faut pas oublier que même si l'érythropoïèse reste normale il est possible que se développe une anémie si la vitesse de destruction périphérique des hématies est augmentée du fait de l'existence ou de l'accentuation d'un phénomène d'hémolyse.

Il est possible que la variation du nombre des hématies ait été masquée par une diminution de la masse sanguine, ou que la baisse éventuelle soit plus tardive (en raison de la longue durée de vie des hématies qui est d'environ 120 jours). Cette dernière hypothèse ne peut être exclue car les numérations sanguines ont été interrompues lors de la fin de la radiothérapie.

De toute façon, l'interprétation classique qui reliait l'anémie observée chez certains malades à l'aplasie des territoires irradiés est certainement insuffisante puisque cette aplasie s'observe constamment même chez les sujets non anémiques.

Malgré l'existence de phénomènes de compensation et une érythropoïèse demeurée normale ou devenue supérieure à la normale, une anémie peut se développer si des phénomènes hémolytiques apparaissent ou s'exagèrent. On sait la fréquence de l'hémolyse chez les cancéreux (SHEETS 1954, SOHIER 1957) et les animaux irradiés (WAGGENER 1958). Une mesure systématique de la vie des globules rouges grâce au chrome radioactif apparaît donc comme une étude complémentaire indispensable chez les sujets anémiques; elle est actuellement en cours.

Il est également possible que chez certains sujets traités les phénomènes de compensation dans les territoires non irradiés ne s'établissent pas ou restent insuffisants. Ce défaut de capacité de réponse des territoires érythropoïétiques correspond alors à une insuffisance médullaire relative (BOIRON 1958). Le Cas 3 évoque un tel processus.

Celle-ci pourrait être dû, soit à une incapacité de la moelle à répondre au stimulus excitateur soit à l'absence ou à l'insuffisance du stimulus c'est à dire à un défaut du mécanisme de compensation.

La nature du mécanisme de compensation demeure encore obscure.

Il est peu probable que la diminution de la production d'hématies puisse déclancher rapidement un mécanisme régulateur car la fraction d'hématies renouvelées par jour étant de l'ordre de 1 %, le déficit de pro

luction, par destruction d'une fraction de l'ordre de 20 % des tissus rythropoïétiques, est très faible.

L'élévation du taux de fer sérique, soit par défaut de récepteur médullaire, soit par accélération de l'hémolyse, peut être évoquée. C'est n phénomène qui devrait survenir rapidement, mais il n'a jamais été décelé chez nos malades.

L'aplasie d'une partie du système médullaire peut laisser disponible pour le reste du système, le facteur humoral de l'érythropoïèse, l'érythropoïétine.

On sait que l'abondance de ce facteur a été trouvée augmentée chez l animal après irradiation totale de l'organisme (LINMAN 1957). Il serait intéressant de rechercher s'il en est de même chez l'homme après irradiation partielle; c'est l'un des buts des recherches que nous nous proposons actuellement.

La sécrétion de ce facteur humoral pourrait d'ailleurs être accélérée par l'une des précédentes causes.

Conclusion

La chute de l'activité fonctionnelle des territoires médullaires irradiés est donc normalement compensée par une hyperactivité fonctionnelle des territoires non irradiés. Cette hyperactivité entraine même parfois une augmentation de l'activité érythropoïétique globale, comme s'il existait un phénomène de surcompensation.

Il semblerait donc qu'une anémie survenant après irradiation pelvienne soit due, non à une aplasie des territoires irradiés puisque ce phénomène est constant, mais à une insuffisance ou à un défaut des phénomènes de compensation qui sont normalement observés.

RÉSUMÉ

La vitesse de renouvellement du fer plasmatique, l'incorporation du fer dans les globules rouges et la fixation du fer dans les territoires médullaires ont été mesurés grâce au fer radioactif (Fe^{59}) chez 9 malades avant et après radiothérapie pelvienne, par télécobalt-thérapie. Après irradiation du sacrum par des doses de 4 000 à 6 000 r, la fixation du radio-fer dans cet organe est trés abaissée. Elle est par contre augmentée dans les tissus érythropoïétiques non irradiés (sternum, vertèbres cervicales). Le renouvellement du fer plasmatique et l'incorporation de fer dans les hématies ne décèlent pas de baisse de l'activité érythropoïétique globale. Celle-ci semble même parfois augmentée.

SUMMARY

The rate of turnover of the plasma iron and the incorporation of iron in the red cells as well as its uptake in the bone marrow were studied with iron-59 in 9 cases before and after pelvic irradiation with a telecobalt unit. After the administration of doses of

4 000 to 6 000 r to the sacrum the uptake of iron-59 in this bone was much lowered bu was elevated in the nonirradiated erythropoietic tissues. The total erythropoietic ac tivity judged from the plasma iron turnover and the incorporation of iron in red cel does not appear to be decreased after irradiation and is sometimes actually increase

ZUSAMMENFASSUNG

Das Verhältnis des Plasmaeisenumsatzes und die Inkorporation von Eisen in d roten Blutkörperchen sowie dessen Aufnahme in das Knochenmark sind mit Fe^{59} in Fällen vor und nach Telekobaltbestrahlung des Beckens studiert worden. Nach B strahlung des Sakrums mit 4 000—6 000 r war die Aufnahme von Fe^{59} in diesem Knoche sehr herabgesetzt, während sie in den nicht bestrahlten blutbildenden Geweben gesteiger war. Die totale erythropoetische Aktivität, beurteilt nach dem Plasmaeisenumsatz und der Inkorporation von Eisen in rote Blutzellen, scheint nach Bestrahlung nicht herab gesetzt zu sein; mitunter ist sie tatsächlich gesteigert.

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BOOK REVIEW

RÖNTGENANATOMIE DER NEUGEBORENEN- UND SÄUGLINGSLUNGE. Von Zoltan Zsebok. Band 82 in Archiv und Atlas der normalen und pathologischen Anatomie in typischen Röntgenbildern. 160 S. 286 Abb. G. Thieme, Stuttgart 1958. DM 75.

This book consists of a complete survey of the basic principles involved in the roentgenologic examination of the lungs of infants. The author points out that pulmonary disease in newborn infants is no inconsiderable factor in the postnatal mortality and, although in about 60 per cent of cases there are few or no clinical signs, the condition can be detected by roentgenography. Detailed descriptions of the normal anatomy of the infant lung, and consideration of the roentgen diagnosis have received wide recognition in the specialised literature; in the present book the author has analysed his experiences in roentgenologic and anatomic studies of 150 human foetal lungs, 1 000 lungs of newborn infants, and 115 foetal lungs of cattle and sheep.

The reader is given an exhaustive description of the variations in shape of the normal thorax, the various phases of development of the bronchial tree and the lungs, the significance of the hilar and pulmonary markings, the variations in size and shape of the thymus, and the roentgen anatomy of the pleurae and diaphragm. Comparative anatomical viewpoints receive well-deserved attention. A special chapter is devoted to the pulmonary arteries and veins but the bronchial blood vessels, on the other hand, are not mentioned; a short but valuable section deals with the lymphatic vessels and lymph nodes in the thorax. The appearance of the heart is treated only incidentally and the cardiac size is estimated from the heart-lung quotient. Among the different organs in the thorax, only the oesophagus has been omitted from the survey. The pathogenesis of postnatal atelectasis is discussed in detail. To the reviewer, the descriptions of the development of the foetal lung and the roentgen anatomy of the bronchial tree, as well as the account of the anatomical relations between the bronchi and pulmonary arteries, are especially interesting. Reproductions of corrosian preparations, several of which are in colour, are an excellent aid to a comprehension of the text. The thymus may cause difficulties in the interpretation of roentgenograms of the lungs of newborn and young infants and the author has endeavoured to throw light, both by a detailed description and numerous illustrations, on the differential diagnosis between the thymus, mediastinal pleurisy, and segmental or lobar atelectasis. His viewpoints do much to clear up misunderstandings although, in the reviewer's opinion, these problems seem to be somewhat too emphasized. All things considered, this work is a valuable contribution to the anatomical realities underlying the roentgenographic structures in the infant thorax. The illustrations are high class and the references have been brought up to date. The book is warmly recommended to all roentgen diagnosticians concerned with infants.

Ulf Rudhe